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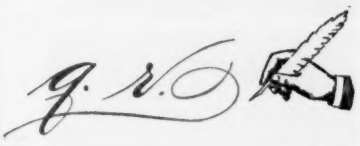

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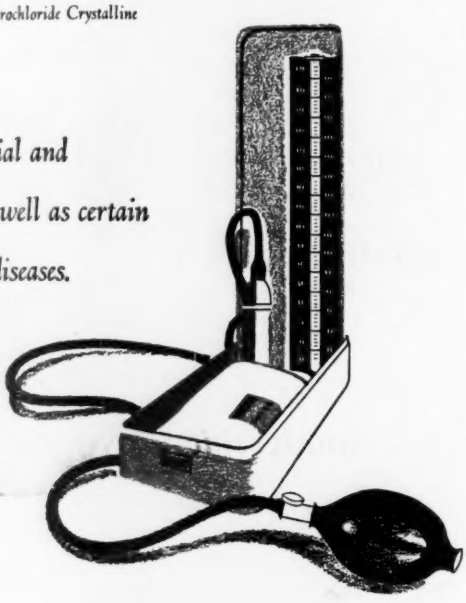

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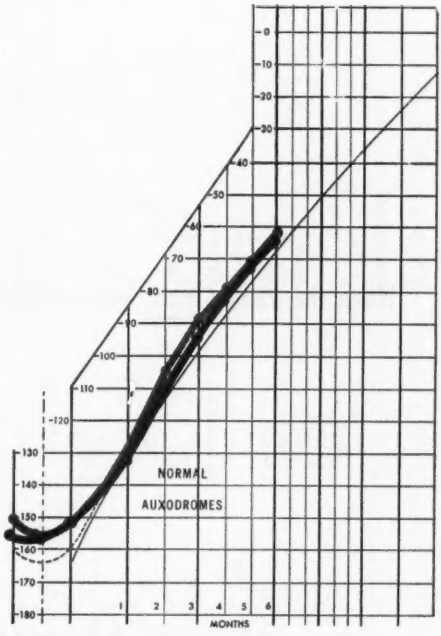
CURVE B

Growth data, recomputed on Wetzel Grid, based on "selected subjects, most of whom were favored by environment;"[2] age: from birth to 6 months.

1. Wetzel, N. C.: J. Pediat. 29:439, 1946.
2. Jackson, R. L., and Kelly, H. G.: J. Pediat. 27:215, 1945.



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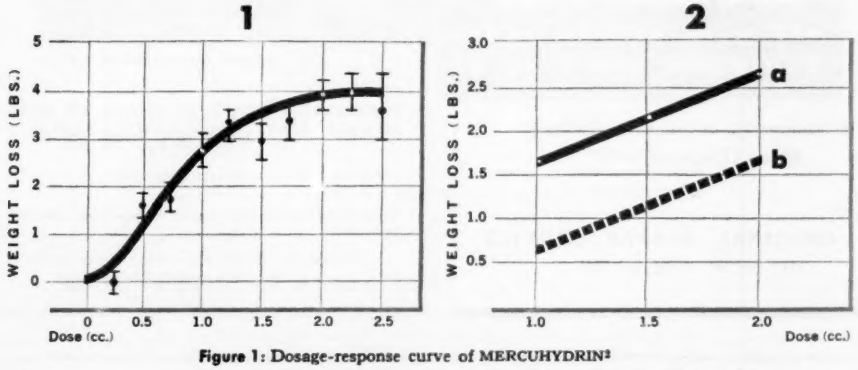

Figure 1: Dosage-response curve of MERCUHYDRIN[3]

Figure 2: Dosage-response curves showing relative diuretic potency of (a) (MERCUHYDRIN) and (b) N-(beta-hydroxymercuri-gamma-methoxypropyl)-2-pyridone-5-carboxylate.[2]

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bibliography: (1) Clarke, D. A.; Modell, W.; Greiner, T.; Kwit, N. T.; Gluck, J. L.; and Gold, H.: The Dosage-Response Curve for the Comparison of Mercurial Diuretics, Am. J. M. Sc. *220*:156, 1950. (2) Cattell, McK.: Dosage in the Therapy of Cardiovascular Disease, J.A.M.A. *144*:889, 1950.

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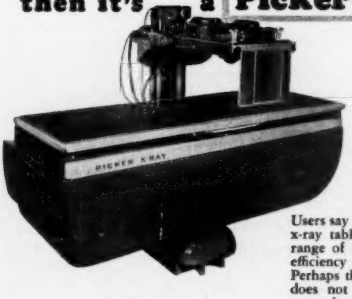

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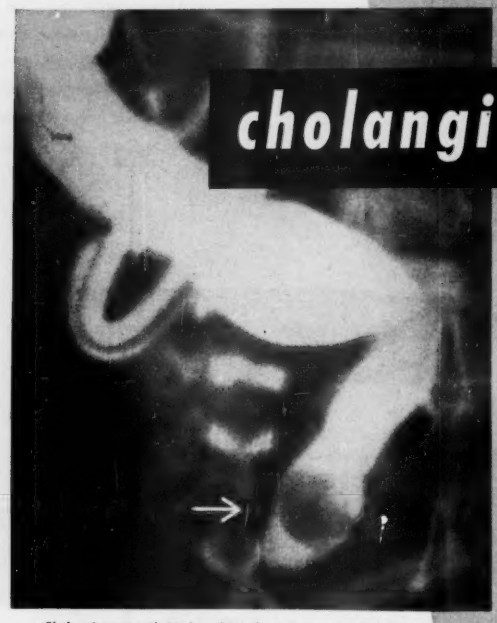

cholangiography

Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

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1. Byrne, R. V.: Amer. Jour. Surg., 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: Amer. Jour. Surg., 78:347, Sept., 1949.

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Volume 245 DECEMBER 6, 1951 Number 23

THE USES OF NUCLEAR DISINTEGRATION IN THE DIAGNOSIS AND TREATMENT OF BRAIN TUMOR*

WILLIAM H. SWEET, M.D.†

BOSTON

IN THE utilization of isotopes to aid in the clinical management of intracranial tumors that has been developed at this hospital in the past few years, we have been aided by many workers. The time at which an elaborate addition to the hospital's investigative facilities is brought into action is perhaps a suitable time to draw attention to the diversity of talents that has been required for making some headway in such a limited field as that of brain tumors.

About four years ago, when Dr. Selverstone and I were receiving our first education in the use of radioactive isotopes from Dr. Solomon and Dr. Hastings at the Biophysical Laboratory at Harvard Medical School, we began to cast about for a radioactive isotope that would concentrate in brain tumors. Dr. Selverstone's suggestion of P^{32} injected intravenously as the phosphate proved magnificently fruitful, and of all the various substances tried here and elsewhere for this purpose, P^{32} gives the greatest differentials between tumor and normal brain in the widest variety of neoplastic types. At the optimal time interval after injection for the maximum differential, twelve to forty-eight hours, even the most slowly growing, sparsely cellular and avascular gliomas have shown useful ratios of greater than 5:1. More cellular or more vascular tumors, or both, have shown ratios even greater than 100:1. As P^{32} decays it emits only β particles, which travel but a few millimeters in tissue. Hence the introduction of an appropriately sensitive probe counter into the brain permits one to ascertain by the counting rate when neoplasm is entered and where its limits are.

Such a probe counter was first designed by the physicist Dr. Charles Robinson, then of Wisconsin. Dr. Solomon promptly secured the aid of Dr. Robinson and his counter, which device we used in man in time to send a telegram with the data to Dr. Selverstone for inclusion in a paper he was presenting at a meeting of the American Medical Association. Dr. Robinson, since then at the Harvard Biophysical Laboratory, has perfected the probe counter so that it is now only 2 mm. in diameter.[1]

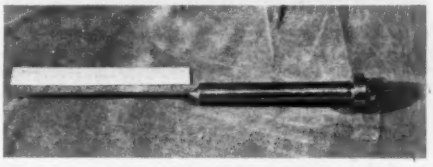

FIGURE 1. *Robinson-Type Probe Counter.*
Only the tiny cylindrical shaft (2 mm. in diameter) enters the brain; the radiation-sensitive portion of this shaft begins 5 mm. from the tip and extends toward the hub for 13 mm.

Figure 1 shows the Robinson type of Geiger–Müller counter that we currently use. The next two figures illustrate the technic for locating and delimiting a brain tumor at operation Figure 2, the photograph of the operative field shows at each lettered point the site of insertion of the Robinson probe counter, and the dotted line shows the plane of resection of temporal and occipital portions of the brain. Table 1 shows the counting rates per minute at a series of depths at each of these points, which gave us the basis for deciding the line of resection. The count rate in the gray matter (at 1 cm.) is higher than that in the underlying white matter, but the counts at B (3 cm.) and E (5 cm.) are those typical of tumor. This patient's tumor was one of the first in the series demarcated with the

*Presented at the dedication of the Research Building of the Massachusetts General Hospital, May 16, 1951.
A review of investigations carried out on the localization of brain tumors at operation with radioactive isotopes in collaboration with Dr. Bertram Selverstone and on the potentialities of their treatment by the products of atomic disintegration at the Brookhaven National Laboratory. Grateful acknowledgment is due to Drs. G. Brownell, M. Javid, C. Robinson, A. K. Solomon and J. C. White.

From the Neurosurgical Service, Massachusetts General Hospital, the Department of Surgery, Harvard Medical School, and the Brookhaven National Laboratory, Upton, New York.

This study has been supported by the Atomic Energy Commission, Contracts AT(30-1) — 1093, AT(30-1) — 730, by funds from an Institutional Grant of the American Cancer Society to the Massachusetts General Hospital and by a gift from an anonymous donor, administered by Dr. J. C. White. The active collaboration of scientific workers at Harvard, Massachusetts Institute of Technology and other institutions is also acknowledged.

†Assistant professor of surgery, Harvard Medical School; associate visiting neurosurgeon, Massachusetts General Hospital.

probe counter; he is still active and symptom free twenty-four months after the removal of his glioblastoma multiforme.

Recently Drs. Selverstone and White[2] have correlated the operative counts in vivo at various points in brain and brain tumor with the actual

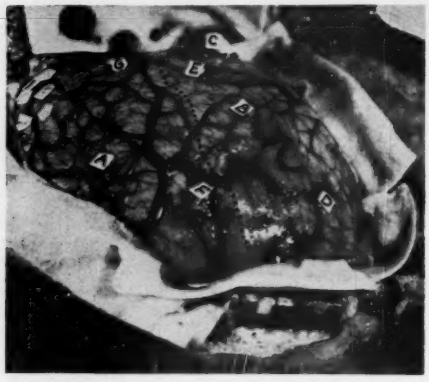

FIGURE 2. *Right Temporoparieto-Occipital Cortex (Patient T.F.). Numbers at upper left corner of exposed area mark sites at which electrical stimulation caused movement of contralateral upper limb.* C, E and B = *temporal lobe;* G, A and F = *parietal lobe; and* D = *occipital lobe.*

site of the counter as determined at autopsy in inoperable cases. They have demonstrated again that the count rate is high when the sensitive part of the counter lies in or adjoining neoplasm. Largely due to Dr. Selverstone's efforts, the use of this instrument has been put on such a firm basis that it forms an integral part of our surgical treatment of many brain tumors. Table 2 shows a summary to date of the results of the method for localizing these tumors at operation.

TABLE 1. *Counting Rates at Different Depths at Sites of Insertion of Robinson Probe Counter.*

No. of Counts per Minute	No. of Hours after Injection (Patient T.F.)					Amount of P^{32} Injected	
Depth	Point A	Point B	Point C	Point D	Point E	Point F	Point G
cm.						millicuries	
1	411	325	—	—	—	—	—
2	248	788*	158	198	236	486†	136
3	38	2483*	66	391†	258	68	148
4	121	—	138	133	476†	118	—
5	53	—	108	—	1123*	—	125
6	—	—	—	—	—	—	26

*Definite tumor count.

†Questionable tumor count.

After removal of the block of tissue to the right of the dotted line in Figure 2, it was found that the counter at point D had passed superior to frank neoplasm; accordingly, the tissue superior to this at point F was left in situ, despite the questionably high count at depth 2 cm.

Efforts have also been made to assist the preoperative diagnosis and localization of brain tumors by detecting a concentration in them of an isotope emitting gamma rays that could penetrate the skull. Here Dr. Selverstone and I[3] have used K^{42}. Although this concentrates to a higher degree in most brain tumors than the other gamma emitter used for this purpose (I^{131} diiodofluorescein), the K^{42} is seized avidly by muscle as well. The medium-sized temporal muscles and the even bulkier suboccipital muscles give rise to a curtain of gamma radiation outside the tumors that lie beneath them. Dr. Selverstone has demonstrated that the obscuration arising from the muscular curtain can be diminished by placing the sensitive counter at a short distance from the skull instead of against it. Still, the procedure bears over muscle an unattractive resemblance to the use of a colorimetric method for finding a black cat behind a pile of coal. On the other hand, for most tumors lying above the muscles, except for the slow-growing astrocytomas, the method appears useful. We have even found one tumor smaller than a cherry just beneath the cortex of the precentral gyrus. This tumor did not deform or shift the lateral ventricle of the ipsilateral hemisphere, yet its excessive gamma radiation after K^{42} administration permitted a correct preoperative localization. The method has also been especially valuable in patients whose brain tumors compressed the lateral ventricle so much that no air would enter it at attempted ventriculography and in other patients with misleading clinical signs.

TABLE 2. *Brain Tumors Localized with Probe Counter Using P^{32}.*

Correct localization (60 demarcated)	105
Uncertain localization	1
False negative (1 avoidable)	4
False positive	4
Total	114

A better method for external localization of brain tumors appears to be in the offing. Matter including living tissue has an annoying tendency to scatter gamma rays; hence the neoplastic image of these rays at the surface of the scalp is considerably blurred and expanded. Dr. Gordon Brownell, of Massachusetts Institute of Technology, now the hospital's physicist, has thought of the tactic of using the special radiation that occurs when a positron strikes an electron and the two particles are annihilated, giving rise to a pair of .51 mev gamma rays, which go off in opposite directions from each other. By means of a coincidence-counting circuit, only those pairs of gamma rays that are not scattered are registered. Figure 3 shows the effectiveness of this technic for eliminating the scattered rays from consideration. It will be seen

that the beam is recorded as a much narrower column when the pairs of annihilation gamma rays from positrons are counted than when directional counting under similar circumstances is tried with I^{131}, the radiation of which is similar in intensity to that of the annihilation gamma ray. We are now

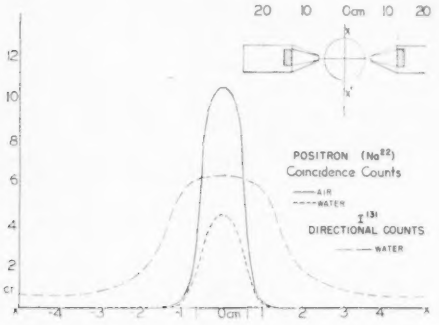

FIGURE 3. *Collimation of Positron Coincidence Counts as Contrasted with I^{131} Directional Counts.*

The diagram in the upper right corner shows a pair of coincidence counters ready to move parallel to the $x-x'$ axis of the head. The zero point on the abscissa of the graph corresponds with the position of the counters in the diagram. Counting rate is indicated on the ordinate. The length of each capsule (one containing the Na^{22} and the other the I^{131}) was 0.5 cm. The much more marked localization of the coincidence counts from the former is clear-cut.

in the process of trying to find the most suitable positron-emitting isotope for this purpose. A group at Duke University, however, had started earlier

TABLE 3. *Activity Ratios of Tissues at Autopsy* $\left(\frac{\text{counts/min./mg. of tissue}}{\text{counts/min./mg. of white matter}}\right)$*

TISSUE	ACTIVITY RATIO		
	CASE 9	CASE 13	CASE 16
Glioblastoma	29.9	54.2	5.5
Blood	—	—	1.8
Skeletal muscle	26.7	15.5	2.6
Cancerous bone (with marrow)	48.6	56.5	4.4
Spleen	41.0	29.9	7.3
Liver	87.6	60.9	10.1

*The intervals between the time of injection and the time of death were, respectively: Case 9, 57.3 hours; Case 13, 62.2 hours; and Case 16, 364 hours.

on the same ideas and has recently published a preliminary communication.[4]

We, with many others, have also been trying to utilize the enormous energies developed at nuclear disintegration to destroy unwanted cells. The huge concentration of P^{32} in brain tumors as compared with normal brain gave rise to an abortive hope that this substance might be of value in therapy, but Table 3 indicates why this has failed. One sees that vital active tissue such as liver and bone marrow take up as much P^{32} as the brain tumors, or more, and that the reason the substance is valuable in tumor localization is that the normal brain takes up so little — rather than that the tumor takes up an extraordinarily large amount. Hence if one is to utilize the blood–normal-brain barrier in designing a treatment of brain tumors one must find some way of concentrating the destructive effect of nuclear disintegration in the brain. The striking tendency of a certain few isotopes to capture slow neutrons and then break up, releasing large amounts of energy, seemed an avenue worthy of exploration, since the beam of slow neutrons can be readily confined to a portion of the head and the other active tissues of the body kept out of harm's way.

ENERGY OF IONIZATION
FOR EACH ISOTOPE IN TISSUE =

$$F \times N \times \sigma_a \times E \times A$$

F = Flux-number of thermal neutrons/cm^2/sec.
N = Number of atoms of an isotope/unit volume.
σ_a = Capture or absorption cross section.
E = Energy in mev after neutron capture.
A = Fraction of this energy absorbed in tissue.

FIGURE 4. *Equation for Computation of Energy Evolved on Neutron Irradiation.*

When a neutron is slowed down to speeds of the order of 2200 meters per second, its energy at that velocity (of only .025 electron volts) is not enough to ionize any atom it happens to meet by knocking off one of its orbital electrons. It reacts with matter chiefly when the nucleus of an atom captures it. The nuclei of the integral atoms of living tissues have only a slight tendency to capture slow neutrons. This cannot be disregarded, however, because there are so many of them, and Figure 5 indicates the type of reaction that occurs on neutron capture by hydrogen and nitrogen, the two most important atoms in living matter in this respect. The same figure indicates the reaction when a $boron^{10}$ atom, which has an enormous capture cross section (σ_a) for slow neutrons, gobbles one up. The high-energy large alpha particle that appears travels less than 15 microns in tissue, which means that its destructive effect is confined to a tiny zone in the immediate neighborhood of the cell containing the boron atom. This reaction caught the attention of Kruger[5] and of Zahl and his co-workers,[6] twelve

years ago; they suggested its use in the treatment of cancer.

When Conger and Giles,[7] at Oak Ridge, reported last year on their radiation of lily bulbs with slow neutrons and showed by computation that a substantial amount of the radiation change in these plants was associated with their trace amounts of boron, Dr. Javid and I[8] decided to try to put enough more boron^{10} into the brain of man that the site of each such atom would largely determine the destructive radiation effect.

With the aid of Dr. Brownell,[9] we have computed to at least a first approximation the radiation dosage arising from each of the elements in brain and brain tumor, according to the simple formula

σ_a	
.33	$H^1 + n \rightarrow [H^2] \rightarrow H^2 + \gamma$ (2.23 mev)
1.7	$N^{14} + n \rightarrow [N^{15}] \rightarrow C^{14*} + p^+$ (.6 mev)
3900	$B^{10} + n \rightarrow [B^{11}] \rightarrow Li^7 + \alpha^{++}$ (2.40 mev)

FIGURE 5. *Chart of Formulas (Slow-Neutron Capture Reactions of Hydrogen, Nitrogen*[14] *and Boron*[10]).

shown in Figure 4. We find that if we can put 50 microgm. of boron^{10} per gm. of tissue into a brain tumor with only 15 microgm. of boron per gm. of normal gray matter (that is, $3\frac{1}{3}$ times as much boron in tumor as in normal brain), the tumor will receive 3 times as much radiation as the brain. In other words, at these levels of boron^{10} concentration the site of this atom largely determines the radiation effect.

With the only substance we have so far tried exhaustively, — borax, — we find that such absolute levels in tumor are readily attainable without producing significant toxic effects and that differentials between tumor and brain of 3:1 to 28:1 occur in some rapidly growing gliomatous and carcinomatous tumors for a short interval up to the first half-hour after injection. We are, of course, attempting to improve our tumor–normal-brain differentials in a wider variety of cases and to maintain this for a longer period.

From here on the work has been continued in collaboration with Drs. Farr, Borst and Van Slyke and their staffs of the Brookhaven National Laboratories. Only if we can make a success of irradiation of patients at the massive Brookhaven nuclear reactor shall we have attained our goal. We are not yet ready to comment on any phase of this major step of the work.

SUMMARY

Research at the Massachusetts General Hospital with isotopes and brain tumors has brought to light several useful findings.

P^{32} concentrates much more in brain tumors than in normal brain; hence a probe-type Geiger–Müller counter detecting beta radiation can be used to advantage to find and delimit such tumors at operation.

K^{42} also concentrates in these tumors; its gamma ray permits external localization through the intact skull in many cases.

The special type of gamma rays emitted when a positron and an electron collide and are annihilated promises to be particularly valuable in the external localization of tumors.

B^{10}, which eagerly captures slow neutrons and then disintegrates, can be concentrated sufficiently in brain tumors to suggest that irradiation with slow neutrons may be useful in their therapy.

REFERENCES

1. Selverstone, B., Sweet, W. H., and Robinson, C. V. Clinical use of radioactive phosphorus in surgery of brain tumors. *Ann. Surg.* **130**:643-650, 1949.
2. Selverstone, B., and White, J. C. Evaluation of radioactive mapping technique in surgery of brain tumors. *Ann. Surg.* **26**:387-396, 1951.
3. Selverstone, B., Sweet, W. H., and Ireton, R. J. Radioactive potassium: new isotope for brain tumor localization. In *Surgical Forum on Fundamental Surgical Problems, American College of Surgeons.* 665 pp. Philadelphia: W. B. Saunders Company, 1951. Pp. 371-375.
4. Wrenn, F. R., Good, M. L., and Handler, P. Use of positron-emitting radioisotopes for localization of brain tumors. *Science* **113**:525-527, 1951.
5. Kruger, P. G. Some biological effects of nuclear disintegration products on neoplastic tissues. *Proc. Nat. Acad. Sc.* **26**:181-192, 1940.
6. Zahl, P. A., Cooper, F. S., and Dunning, J. R. Some in vivo effects of localized nuclear disintegration products on transplantable mouse sarcoma. *Proc. Nat. Acad. Sc.* **26**:589-598, 1940.
7. Conger, A. D., and Giles, N. H., Jr. Cytogenetic effect of slow neutrons. *Genetics* **35**:397-419, 1950.
8. Sweet, W. H., and Javid, M. Possible use of neutron capturing isotopes such as boron^{10} in treatment of neoplasms: intracranial tumors. *J. Neurosurg.* (in press).
9. Javid, M., Sweet, W. H., and Brownell, G. Possible use of neutron capturing isotopes such as boron^{10} in treatment of neoplasms: computation of radiation energies and estimation of effects in normal and neoplastic brain. *J. Clin. Investigation* (in press).

IDIOPATHIC THROMBOPENIC PURPURA IN CHILDHOOD*

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THE syndrome of "idiopathic" or "primary" thrombopenic purpura has been discussed by a number of authors,[1-4] but these studies usually have included all age groups or have used large subdivisions of age ranges. The condition as it is seen in childhood has not been dealt with specifically or in detail for some time. McLean[5] in 1932 reported a short follow-up study of 21 cases, and Diamond[6] briefly summarized the results of therapy in 28 cases in 1938. Since then, except for studies on congenital purpura,[7] no comprehensive publications have appeared on thrombopenic purpura in childhood.

This paper reports on 47 cases§ of idiopathic purpura in children seen during a ten-year period at the Children's Hospital of Michigan, with the purpose of presenting the characteristics of the clinical picture and course as they are seen in this age group, and of stressing differences in the condition in children as compared to its manifestations in adults.

CASE MATERIAL AND METHODS

The patients were children admitted to the wards or, rarely, studied as ambulatory patients in the Anemia Clinic. The criteria for the diagnosis of primary thrombopenic purpura were: significant thrombopenia with platelet counts below 100,000, associated with clinical evidence of an abnormal bleeding tendency. These findings were nearly always supplemented by one or more of the following: prolonged bleeding time; delayed, incomplete or absent clot retraction; and increased capillary permeability.

Confirmation of the diagnosis and exclusion of other conditions was obtained by bone aspiration in the last 30 cases of the series. Cases of purpura associated with primary diseases such as leukemia, aplastic anemia, disseminated tuberculosis and so forth were excluded from this series, as were all cases of nonthrombopenic purpura.

The patients were followed closely during the initial episode of purpura until all abnormal manifestations had disappeared. Most of the children were subsequently seen at regular intervals. Those patients admitted in the early days of the study who had not been followed closely after the subsidence of their original symptoms were called in for a complete review at the end of the ten-year period. At this time a detailed history relating to bleeding manifestations, allergies and other pertinent information was obtained, and a complete physical examination and hematologic study were made. These data were supplemented as indicated by the records of physicians whom the patients had consulted or hospitals where they had been studied before or after their contact with us. The total period of follow-up of the patients in this study was at least six months in 42 cases and exceeded two years in 27 of these.

Platelet counts were determined by the Fonio method. In a few cases in which platelets were obviously diminished or virtually absent the degree of thrombopenia was determined only by scanning routine peripheral-blood films.

Bleeding time, clotting time and capillary fragility were determined by the various members of the resident staff; consequently the technic varied somewhat. Bleeding times were determined by the Duke method, clotting times by the Lee–White method and determinations of capillary fragility by maintaining a blood-pressure cuff at a pressure halfway between diastolic and systolic for five minutes. Clot retraction was estimated by observing at twenty-four and forty-eight hours clotted blood kept at 37°C. Heparin-tolerance tests were done by a modification of the Allen method.[8]

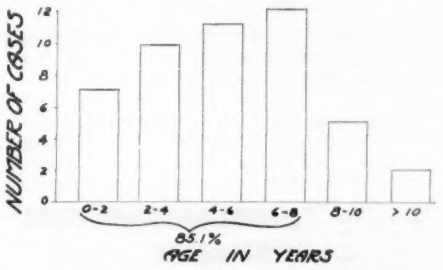

FIGURE 1. *Age Incidence in 47 Cases of Idiopathic Purpura.*

OBSERVATIONS

Clinical Features

The age incidence of thrombopenic purpura among our patients ranged from nine days to eleven years (Fig. 1). (The upper age limit for admission to the hospital is twelve years.) The mean age was 5.3 years. Almost 60 per cent of the cases occurred in children between the ages of three and seven years.

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§This group does not include patients treated with cortisone during the past year. These will be the subjects of a later report.

There were 28 boys and 19 girls, a ratio of 1.4:1, which stands in contrast to the sex incidence of purpura in adults, with its well known predominance of women. Forty-one children were white and 6 were Negroes.

A seasonal incidence was suggested when the dates of onset of the initial bleeding episodes were

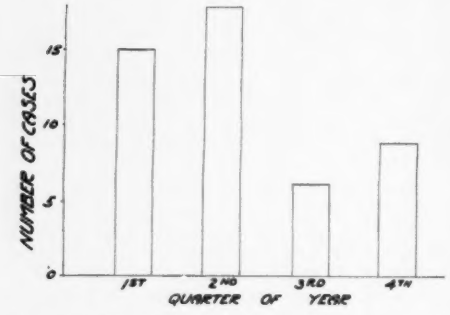

FIGURE 2. *Seasonal Incidence of Onset of First Episode in 47 Cases of Idiopathic Purpura.*

plotted (Figure 2). The smallest number of cases were seen in the late summer and fall. Thereafter there was steady rise, with a peak incidence in the late spring.

Purpura in children is often regarded as a postinfectious manifestation. A history of antecedent

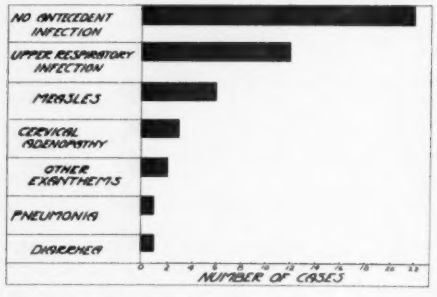

FIGURE 3. *Incidence of Antecedent Infection in 47 Cases of Idiopathic Purpura.*

infection within several weeks prior to the onset of bleeding could not be obtained, in spite of careful questioning, in 22, or 46.8 per cent, of the cases (Figure 3). In many of the remaining patients the antecedent illness had been trivial, consisting in infections of the upper respiratory tract — usually mild coryza, sore throat or the like. In 6 patients measles had preceded the onset of purpura by an interval ranging from five days to five weeks. The course of the measles had not been unusual in any of these patients, as far as could be ascertained from the history. The relation between measles and thrombopenic purpura was mentioned by Karelitz[9] and has recently been stressed by Ackroyd.[10] However, if there is any etiologic relation between the two conditions, purpura must be an extremely rare sequel of measles, in view of the universality of this infection.

Attempts have been made to interpret thrombopenic purpura, as has been done with anaphylactoid purpura, as a sensitivity phenomenon of allergic nature. A detailed history with respect to the usual allergic phenomena was taken in 44 of the 47 cases. In 9 patients, or 21 per cent, some form of allergy had been present at some time — though in no case at the time of the purpura. The allergic manifestations were hives in 6 cases. Two children had asthma and 1 had had infantile eczema. The allergens were not known in any of these cases. In only 3 of the children with allergic manifestations was there a history of allergy in another sibling. In 10 other cases a member of one of the two preceding generations of the family was said to have an allergy.

A detailed family history concerning bleeding tendencies was available in 40 cases. Impressive evidence of a familial bleeding disorder was obtained in only 1 child with 2 cousins, children of 2 maternal uncles, who had died of hemorrhage in early childhood. In 3 cases one of the parents was said to have frequent nosebleeds. The maternal grandfather of another child was said to have suffered from frequent nosebleeds but to have been cured by an operation. A tendency to bruise easily was recorded in the uncle of still another patient. Thus evidence for a hereditary bleeding diathesis in the group as a whole was virtually lacking.

Physical examination rarely yielded abnormal findings other than the hemorrhages themselves. Splenomegaly was encountered only once. In 5 children the tip of the spleen could be palpated at the costal margin on inspiration. In the child with splenic enlargement the size of the liver was also significantly increased. These findings raised doubts of the diagnosis at the time, but the bone-marrow examination disclosed no evidence of leukemia, the anemia seemed proportionate to the blood loss, the course was not unusual and the liver and spleen receded with improvement. Lympadenopathy was not found in any patient in the group.

The localization of the hemorrhages is of interest. Petechial hemorrhages and ecchymoses in the skin occurred in all but 1 case. In 21 patients cutaneous hemorrhages combined with petechial bleeding in the oral and conjunctival mucous membranes were the only demonstrable manifestations of an abnormal bleeding tendency. This type of bleeding occurred in combination with epistaxis in 14 other children.

Cutaneous purpura was accompanied by bleeding from one other major internal source in 5 cases — the urinary tract in 2, the central nervous system in 2 and the gastrointestinal tract in 1 patient. In 6 cases bleeding at multiple sites, including the skin, was noted. One child had melena, hematuria and epistaxis but no cutaneous bleeding.

Bleeding into the central nervous system occurred in 4 patients. Two of these died; at autopsy they were found to have a hemorrhagic encephalopathy, with multiple petechial pericapillary hemorrhages obviously related to an acute necrotizing vasculitis. Pathologic changes of this type do not seem to have been reported in association with primary purpura[11] but conform to the picture most often seen in syphilitic patients treated with arsenicals and known as hemorrhagic encephalitis. We are inclined to regard these two cases as instances of the latter condition complicated by thrombopenic purpura rather than as of primary purpura. Since in each case there was gross hemorrhage, — subdural or cerebral, — and since the early clinical manifestations and laboratory findings were indistinguishable from those observed in primary purpura, the cases are included in this report in order to avoid arbitrary selection.

In the two other patients, bleeding into the central nervous system was suggested by convulsions and the presence of xanthochromia or blood in the cerebrospinal fluid. One patient recovered but subsequently had recurrent generalized convulsions, probably on the basis of damage caused by the cerebral hemorrhage; the other had a transitory hemiplegia.

Thus, if one excludes the two cases in which the bleeding was found to be related to a necrotizing vascular process, central-nervous-system hemorrhage developed in only 2, or 4.4 per cent, of the children. This incidence stands in contrast to the recent report of Elliott,[2] who found bleeding in this area in 12.9 per cent of 93 patients ten years of age and older.

Five children developed hematuria; 4 had gastrointestinal bleeding and one had vaginal bleeding. The bleeding was severe in some instances, leading to a profound acute anemia, whereas in other cases the hemoglobin levels were scarcely or not at all affected. There was no correlation between the severity of the initial bleeding episode and the intensity or duration of subsequent hemorrhagic manifestations.

Laboratory Findings

In all cases the platelet count was less than 60,000, and in most instances the platelets were virtually absent. The bleeding time was invariably prolonged. The clotting time of venous blood was normal in 42 patients in whom the test was made and was slightly prolonged in one case. Clot retraction was delayed and poor or absent in 23 of 29 cases but was reported as complete in twelve to forty-eight hours in the remaining 6. Capillary permeability was definitely increased in 23 of 32 patients.

Anemia of significant degree (hemoglobin levels below 10 gm. per 100 cc.) was encountered in 25 per cent of the cases and was severe in almost 50 per cent of these. Lymphocytosis was not a constant finding but occurred in approximately 30 per cent of the cases. No instance of leukopenia was encountered.

Bone-marrow aspirations were done in 30 cases. A uniform or diagnostic pattern was not evident with the technics used, although certain suggestive features were frequently seen. With a crude survey technic on smears made of the first drop of liquid marrow obtained, an attempt was made to estimate in a rough quantitative manner the number of megakaryocytes. As many smears as possible were made and examined with special attention to the "feather edge" where megakaryocytes are apt to aggregate. On this basis a distinct increase in the number of megakaryocytes was thought to be present in 11 cases.

In 4 cases the number of megakaryocytes was thought to be normal; in 8 others a decrease seemed evident. In 7 cases the specimen was judged unsatisfactory for purposes of megakaryocyte study. Although the majority of the marrows exhibited megakaryocytes with the features of immaturity, lack of granular development and poor platelet formation as described by Dameshek[12] and others,[13] these findings were not invariably present and could not be correlated with the course of the disease.

The bone-marrow "eosinophilic index" of Schwartz[14] was determined in 28 cases in an attempt to make prognostic correlations. Schwartz, reporting on a series of 100 cases of all age groups, found a high eosinophilic index (more than 50 eosinophils in 1000 granulocytes of metamyelocyte, band-form or mature-leukocyte character) to be associated with a benign self-limited type of purpura. By contrast, cases with a low index tended toward recurrence and frequently required splenectomy.

Our findings with respect to the eosinophilic index showed no clear-cut correlation with the course of the disease and therefore had no prognostic value. Exactly 50 per cent of the marrows examined had indices greater than 50. With respect to duration, a low index was found in 7 of the 18 children whose purpura lasted for less than 3 months, whereas 2 of 6 children with a more chronic course had a high index. As regards recurrence rate, high and low indices were almost evenly distributed among the patients who did not relapse. However, in the small group of patients with recurrence the majority had a low eosinophilic index.

Heparinoid-substance levels, as evaluated by the heparin-tolerance test, were obtained in 4 cases and showed no significant elevations compared to normal controls.

Course

The management of the patients was guided by the severity and duration of the bleeding manifestations. Blood transfusions were given to 27 patients chiefly on the indication of anemia or continued blood loss. Bank blood, stored in ACD solution, was used except in one case in which 2 direct transfusions were given. Apart from its effect on restoring hemoglobin, transfusion did not seem to affect the condition. There was no consistent rise in the platelet count and no appreciable effect on capillary fragility or in clinical bleeding manifestations.

Although improvement followed transfusion in some cases, the same degree of improvement was frequently observed in patients who had not received transfusions. Conversely, transfusions often failed to affect the bleeding state to any appreciable degree.

In the earlier years of the study vitamin C, vitamin K, folic acid, rutin, liver extract and pentnucleotide had been used without demonstrable effect. In recent years 2 patients received lysine by mouth without improvement. The majority of the patients received no therapy other than transfusions, as indicated, and occasional local hemostasis.

Splenectomy was performed in 7 cases. The indications varied, as some of the patients were under the care of the referring physicians.

The duration of the bleeding manifestations was surprisingly short in the majority of cases. Among 42 patients who were followed for six months or longer the bleeding subsided in 29 cases within a month and within eight to ten days from the onset in several. In 6 additional patients the purpura lasted intermittently or constantly for less than three months but more than one month. In one additional child bleeding continued for a period of three months. In 6 patients the disease ran a chronic course extending beyond six months in duration. The longest period of more or less continuous purpuric manifestations was three years.

A splenectomy was performed on this patient thirty-nine months after onset of symptoms. Postoperatively there was cessation of all bleeding symptoms, but the platelet count showed only a transient rise and has remained at pathologic levels for four years. The bleeding time, however, was normal at the end of that period, and there have been no abnormal bleeding manifestations. The patient was menstruating without undue blood loss.

The usual pattern of spontaneous recovery was characterized by cessation of clinical bleeding manifestations, usually with return of capillary fragility at the same time or even slightly earlier. This was followed in most cases by a somewhat gradual rise in the platelet count and return to normal bleeding time and clot retraction. In some instances there was a prolonged lag between the disappearance of clinical purpura and the return of platelets. Two representative cases are reported.

Case Reports

Case 1. A. R., a 6-year-old girl, was admitted to the hospital with a history of developing many ecchymoses and petechiae and passing bloody urine for 3 to 4 days. The peripheral blood showed no abnormality except a moderate anemia and an almost complete lack of platelets. Bone-marrow aspiration showed normal erythropoiesis and leukopoiesis. Capillary fragility was greatly increased and the bleeding time was 20 minutes.

The patient received two blood transfusions for anemia and continuing blood loss. The capillary fragility and bleeding time and the platelet counts were followed serially. The hematuria stopped about 10 days after the onset of symptoms, but cutaneous hemorrhage continued to appear. At that time the abnormal capillary fragility had become less marked and the bleeding time was normal. The thrombopenia continued. On the 16th day of the disease oozing of blood from nose and ears was observed, and the bleeding time again was elevated. At this time the capillary fragility, however, was less abnormal than before. It became normal at about the 23rd day, by which time the bleeding time had returned to normal limits.

All bleeding stopped approximately on the 25th day. The bleeding time was normal and the capillary fragility remained negative. The platelet count, however, remained low and did not rise until 3 months after the first onset of symptoms. The child has been followed over a 4-year period and has had no further recurrences of bleeding.

Case 2. M. McP., a 3-year-old Negro girl, entered the hospital with a 24-hour history of epistaxis of severe degree. No cutaneous purpura or other bleeding was present. There was marked anemia and almost complete absence of platelets. Results of a bone-marrow aspiration were compatible with the diagnosis of idiopathic thrombocytopenic purpura. Bleeding time on admission was greater than 25 minutes. The capillary permeability was not determined at this time. Because of the anemia the child was given several blood transfusions. On the second hospital day a capillary-fragility test was found to be negative. The epistaxis continued and hematuria and melena developed. On the 3rd hospital day the bleeding manifestations abruptly ceased. On the 5th hospital day the bleeding time was 5 minutes; from that time on it remained normal. The platelet count began to rise on about the 6th hospital day. In 3 weeks the count had become normal. No further bleeding has occurred over a period of 1½ years.

Bone-marrow aspirations were obtained on the 2nd, 4th, 6th, 9th and 23rd days of the disease. No peripheral aggregation of platelets was seen in the megakaryocytes until the aspiration of the 23rd day.

Results of Therapy

Of 40 patients treated conservatively (Fig. 4), 2 died within a few days after the onset. These 2 cases have been referred to earlier. The onset of purpura was preceded by scarlet fever in 1 case and was without antecedent illness in the other. In the postscarlatinal case the original illness had been followed 3 weeks later by a recurrence of sore throat, for which the child had received sulfapyridine. At this time he began to complain of multiple joint pains and swellings and had several episodes of epistaxis. Ten days later purpura had begun, and the child died 3 days afterward. The autopsy disclosed a generalized acute and subacute arteriolitis, characterized by necrosis and inflammatory cell infiltrations in the vessel walls. There was gross cerebral hemorrhage, as well as hemorrhage in the thymus, anterior mediastinum and bladder, and

thrombosis of the lateral dural sinus and embolism of a branch of the pulmonary artery. An acute splenitis was also present.

The history and the character of the lesions seem to indicate a sensitivity phenomenon related to a streptococcal infection and possibly to drug therapy and set the case apart from ordinary uncomplicated purpura.

The second death occurred in an eighteen-month-old girl who had been well until the sudden onset of coma, followed sixteen hours later by purpura. She died twenty-four hours later. Grossly there was massive subdural hemorrhage as well as petechial hemorrhage in many sites. Histologic examination showed arteriolar and capillary necrosis, with perivascular hemorrhage throughout the brain, spinal cord, meninges and choroid plexus. Tissues from other parts of the body showed no vascular alterations. Again the primarily vascular nature of the disease seems beyond question, and it is clear that neither of the 2 cases represents an ordinary uncomplicated purpura. It appears highly doubtful that splenectomy could have altered the outcome of an illness characterized by widespread fixed vascular lesions.

These 2 cases represent a mortality of 5 per cent among 40 conservatively treated patients. Of the 38 survivors, 35 have been followed for at least six months. In 32 of these the initial episode was not followed by recurrences. The purpura in these patients was an acute, benign, self-limited condition that subsided with supportive therapy or without treatment. The longest period of purpuric manifestations in this group was three months.

In 3 cases purpura recurred at intervals ranging from four months to one and a half years. One of these patients was again treated conservatively and has remained free of purpura for four years. The other 2 patients were unavailable for follow-up study after the recurrence.

The experience gained with the entire group of medically treated patients indicates that purpura is usually a disease of short duration in children, recurs rarely and even after recurrence may subside spontaneously.

If the cases treated by splenectomy are reviewed against this background the results of the operation are not overly impressive. Of 7 patients treated by splenectomy, 1 died. The mortality in this small group is 14.4 per cent. The patient was an 11-year-old girl whose bleeding had become severe and prolonged and who was subjected to the operation even though a bone-marrow aspiration had shown the virtual absence of megakaryocytes. There was no striking postoperative rise in platelets, and the patient died three weeks later with uncontrollable bleeding. At autopsy, massive hemorrhage into the peritoneal and pericardial cavities as well as innumerable smaller hemorrhages into virtually every tissue of the body were found, but no vascular lesions could be demonstrated. The surgically removed spleen had shown no diagnostic features.

In 3 of the 6 children now alive who underwent splenectomy, the platelets rose immediately, the bleeding stopped and there was no recurrence. One of these patients had had purpura for only nine days at the time of the operation, a period in which spontaneous recovery is the rule. There had been no unusually severe or threatening bleeding. The other 5 patients whose spleens were removed had had purpura for longer periods of time, ranging from two and a half months to three years.

In 3 cases splenectomy must be regarded as a partial or complete failure. Although in one of these patients the immediate effect of the splenectomy was a rise in platelet counts and cessation of bleeding, a frank clinical relapse of purpura occurred two months later. In the second case, already referred to above, the platelets soon fell to subnormal levels (50,000 or less), the bleeding time was prolonged and capillary fragility remained increased, but there was no clinical recurrence of bleeding for at least four years.

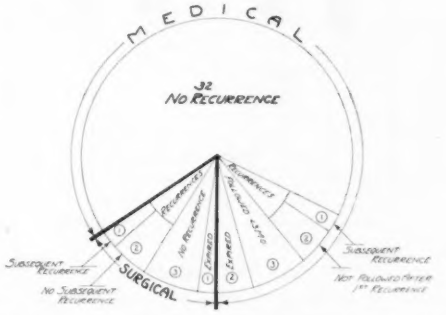

FIGURE 4. *Results of Treatment in 47 Cases of Idiopathic Purpura.*

In the remaining survivor of this group splenectomy failed to produce either a rise in platelets or a cessation of the bleeding tendency. The purpura continued and the platelets were diminished for one year, after which time the bleeding stopped and the platelets returned to normal values.

DISCUSSION

Our findings indicate that the syndrome of idiopathic purpura in children differs from that in adults in several significant respects. In the majority of cases thrombopenic purpura appears to be a benign self-limited condition of short duration. Evidence for a hereditary factor is extremely scanty in our case material. The characteristic predisposition of females toward purpura is not apparent

in this group. A tendency toward a seasonal incidence of childhood purpura is indicated by our findings. Cerebral hemorrhage is uncommon.

The analysis of 47 cases furnished no conclusive evidence in favor of an allergic background of thrombopenic purpura in childhood. The frequency of even trivial infections was likewise insufficient to establish a causal relationship, except possibly in the case of measles.

Bone-marrow examination disclosed no consistent pattern that could be correlated with the course or prognosis with respect to quantitative or qualitative changes in the megakaryocytes or with respect to eosinophilia. However, in the only patient in whom a complete absence of megakaryocytes was demonstrated, the results of splenectomy were disastrous;

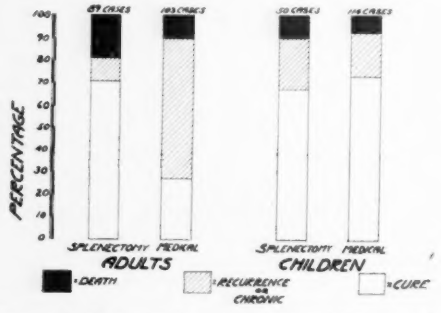

FIGURE 5. *Results of Treatment of Idiopathic Purpura in Adults and in Children.*

splenectomy therefore seems contraindicated in such a case.

The results of splenectomy do not indicate a clear-cut advantage of surgical over medical management. These results must be evaluated against the background of the natural course of the disease in children. Early in the disease the expectation is for spontaneous recovery, and splenectomy done at this stage cannot be properly evaluated. It seems to us that early splenectomy should be avoided except possibly in cases of bleeding of threatening degree or of critical location. In this belief we are in essential agreement with Diamond,[6] Elliott,[1,2] Rosenthal[3] and McLean.[5]

Comparison of the results of splenectomy with those of conservative management in the few more chronic cases is not conclusive. Few patients, naturally, were allowed to go without splenectomy if their course became chronic, and only one of these could be followed long enough to observe the outcome. This child eventually had a spontaneous, lasting remission comparable in every respect to that seen after splenectomy. Of the 5 splenectomized patients with chronic purpura only 2 were cured after the operation.

Figure 5 shows a comparison of the results of treatment of thrombopenic purpura reported in several large series of adult patients and of children, compiled from the literature. The columns for children include our own cases as well. It is clear that in children the recurrence rate is no higher—in fact, is slightly lower in the "medical" than in the "surgical" group. Allowing for the fact that a certain amount of selection determined the choice of splenectomy (in that only patients with severe or chronic purpura would usually undergo operation), the higher death rate and recurrence rate on patients whose spleen had been removed argues against relying too strongly on this procedure. At present adequate criteria for splenectomy in purpura of childhood do not seem to exist. As the value of the operation in childhood is doubtful, it seems to us that conservatism is indicated.

SUMMARY

The natural history of idiopathic thrombopenic purpura in children was studied on the basis of data on 47 patients, the majority of whom were followed for a significant period of time.

Children between the ages of two and eight years were found to be most frequently affected.

In the majority of the cases, the disease as seen in children appears to be a benign self-limited condition of short duration. Idiopathic thrombopenic purpura in childhood further differs from the condition as seen in adults in that it shows no sex predilection and is rarely familial.

A clear-cut relation to antecedent infection or to allergy could not be demonstrated. There was a suggestive tendency toward a seasonal incidence in idiopathic thrombopenic purpura, the peak of cases occurring in the spring.

The material studied yielded no consistent findings in the bone marrow with regard to either megakaryocytes or degree of eosinophilia. No prognostic correlations concerning idiopathic thrombopenic purpura could be derived from the study of the marrow, although for the exclusion of other primary diseases affecting the marrow aspiration is essential.

Adequate criteria for splenectomy in idiopathic thrombopenic purpura of children have not been established. Viewed against the background of the natural course of the disease, successful results in cases treated by early splenectomy cannot be attributed to the operation, since spontaneous recovery is the rule. In chronic cases, splenectomy may or may not result in a cure. Splenectomy in children should probably be reserved for cases of uncontrollable bleeding and chronic recurrent purpura.

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REFERENCES

1. Elliott, R. H. E., Jr. Revaluation of splenectomy in thrombocytopenic purpura, based on 27 year combined clinic follow-up experience. *Proc. Inst. Med. Chicago* **16**:330-344, 1947.

2. Elliott, R. H. E., Jr., and Turner, J. C. Splenectomy for purpura hemorrhagica. *Surg., Gynec. & Obst.* **92**:539-544, 1951.
3. Rosenthal, N. Course and treatment of thrombocytopenic purpura. *J. A. M. A.* **112**:101-106, 1939.
4. Wintrobe, M. M., Hanrahan, E. M., Jr., and Thomas, C. B. Purpura hemorrhagica, with special reference to course and treatment. *J. A. M. A.* **109**:1170-1176, 1937.
5. McLean, S., Kreidel, K., and Caffey, J. Hemorrhagic thrombocytopenia in childhood: clinical study of 21 cases. *J. A. M. A.* **98**: 387-393, 1932.
6. Diamond, L. K. Indications for splenectomy in childhood: results in 51 operated cases. *Surgery* **39**:400-421, 1938.
7. Robson, H. N., and Walker, C. H. M. Congenital and neonatal thrombocytopenic purpura. *Arch. Dis. Child.* **26**:175-183, 1951.
8. Allen, J. G., et al. Some observations on bleeding tendency in thrombocytopenic purpura. *Ann. Int. Med.* **27**:382-395, 1947.
9. Karelitz, S. Measles. In Holt, L. E., Jr., and McIntosh, R. D. *Diseases of Infancy and Childhood.* 1421 pp. New York: Appleton-Century Company, 1940. P. 1134.
10. Ackroyd, J. F. Three cases of thrombocytopenic purpura occurring after rubella, with review of purpura associated with infections. *Quart. J. Med.* **18**:299-318, 1949.
11. Hertzog, A. J. Essential thrombocytopenic purpura: autopsy findings in 36 cases. *J. Lab. & Clin. Med.* **32**:618-621, 1947.
12. Dameshek, W., and Miller, E. B. Megakaryocytes in idiopathic thrombocytopenic purpura, form of hypersplenism. *Blood* **1**:27-51, 1946.
13. Diggs, L. W., and Hewlett, J. S. Study of bone marrow from 36 patients with idiopathic hemorrhagic (thrombopenic) purpura. *Blood* **3**:1070-1104, 1948.
14. Schwartz, S. O., and Kaplan, S. R. Thrombocytopenic purpura: prognostic and therapeutic value of eosinophil index: analysis of 100 cases. *Am. J. M. Sc.* **219**:528-533, 1950.

CONGENITAL ARTERIOVENOUS FISTULATION OF THE LOWER LIMB*

Report of a Case Successfully Treated by Total Excision

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FAILURE of endothelial closure between primordial arteries and veins results in a complex of multiple arteriovenous shunts without intervening capillary bed. As compared to the simple traumatic variety, these congenital shunts are almost always multiple, and the term "fistulation" is hereinafter used to emphasize this multiplicity. Considering the intricacies of vascular embryology, it is remarkable that the condition is not more frequently seen. By the time it is discovered, congenital fistulation is usually already slowly expanding and has become destructive. By pressure erosions, nonmalignant "invasion" of adjacent muscle, bone, nerves and other structures gives rise to the false impression of vascular neoplasia. Only with surgical excision can one hope for more than a temporary delay of a progressive threat to life or limb,[1-8] yet it is among the surgical cases that many failures have occurred, with recurrence and the necessity of amputation, or exsanguination. Callander[4] in 1920 found 3 congenital cases among 447 arteriovenous fistulas of all types in all locations. Seventy-nine congenital cases[1,2, 5-28] of fistulation limited to the lower limb were found since that time to include but 4 surgical cures. These cases are reviewed (Tables 1 and 2), and an eightieth case, the fifth to be successfully managed by total resection, is presented.

There is general agreement[1, 8, 29-32] that angioma simplex, cavernous, racemose, serpentine and cirsoid angiomas or aneurysms, diffuse phlebectasia, congenital arteriovenous fistula and the more recent syndrome, "arterial varices" involving the saphenous system,[31] all represent original developmental arteriovenous fistulas. These numerous confusing terms are merely superficially descriptive of the end result, arteriovenous fistulation, common to all. End results thus superficially described are largely determined by the number and degree of freeness of anastomosed constituents, the stage in vascular development in which they occurred and the stresses and strains to which they were subjected.

Diagnosis of congenital arteriovenous fistulation depends on demonstration of multiple shunts and is suggested by their effects, when these shunts are significantly free. This may be accomplished by anatomic demonstration at operation or autopsy,

TABLE 1. *Diagnostic Signs in 79 Cases of Congenital Arteriovenous Fistulation of Lower Limb.*

	Present	Absent	Not Mentioned	Total
Trophic changes	29	26	24	79
Bruit	21	49	9	79
Thrill	17	49	13	79
Cardiac enlargement	11	17	51	79
Surface-temperature increase	43 (av. 2.9°C.)	—	36	79
Oxygen-saturation increase	31 (av. 24.6 v /0)	—	48	79
Limb hypertrophy	29 (av. 3.2 cm.)	22	17	68*
Bradycardiac reaction	11 (av. 14 beats /min.)	11	57	79

*Nine additional cases were reported as "increased"; strangely enough, in two cases the involved limb was shortened by 3 and 1.5 cm. respectively.

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or radiologic demonstration by bone erosion or angiography, and is suggested by certain nonspecific signs of a disturbed circulation (Table 1).

Table 2 sets forth results in the 79 cases according to mode of treatment. These results have been poor; indeed, no attempt at cure was made in most of the cases. This is understandable, since the majority have been unfavorable complex multiple shunts, almost invasive in nature, involving large proportions or all of a given extremity. The choice was often between no treatment at all and a major amputation. In only 18 of the 79 cases was radical surgery attempted for cure; 7 of these, or nearly half, resulted in amputation. There were but 4 cures.

TABLE 2. *Summary of Results in Treatment of 79 Cases of Congenital Arteriovenous Fistulation of Lower Limb.*

No. of Cases	Treatment	Results				
		No follow-up	Cured	Improved	Unsatisfactory	Amputated
26	Palliation (conservative treatment)	1	0	21	3	1
11	Palliation (combined with surgery)	1	0	4	1	5
18	For cure: surgery	4	4	2	1	7
4	No treatment	2	0	0	2	0
20	Treatment not mentioned	20	0	0	0	0
79		28	4	27	7	13

Case Report

Mrs. K. S. (W. M. H. 72602), a 30-year-old woman, was seen in consultation at the Wesson Memorial Hospital on April 23, 1950, for a painful mass in the right groin of 2 days' duration.

Three months previously she had undergone appendectomy and right salpingo-oophorectomy for a cyst of the right ovary. Two days before admission she experienced a sudden sharp pain in the right groin. Her attention was thus directed to a groin mass, which she denied ever having seen before. Previous trauma was denied, as was exertional dyspnea or any unusual exercise intolerance. Two days after its first discovery, when a needle was introduced into the mass by a physician, copious bright-red (oxygenated) blood under pressure pushed the piston out of the syringe. During the ensuing several hours the same mass increased in size and became more painful, with sharp intermittent stabs of pain, and the patient was hospitalized.

Nothing abnormal was noted on general physical examination, except for a bizarre and unusual large tortuous varix running up the posterior aspect of the right leg and disappearing into the posterior portion of the vagina. This varix did not pulsate. The blood pressure was 120/80. Just below and medial to the right anterior superior iliac spine was a rounded, firm, nontender protuberance under the skin, 5 cm. in diameter. A small puncture wound, the site of the recent diagnostic aspiration, was seen on its summit. Palpation revealed markedly expansile systolic pulsations but no thrill. Auscultation of the mass revealed a continuous loud whirring bruit with systolic accentuation that became louder as the stethoscope was transferred medial to the mass to a point overlying the right femoral triangle. Similar auscultation on the opposite side failed to elicit a bruit.

The peripheral pulses were normal and equal bilaterally. No trophic or other skin changes were noted on the leg. The skin temperatures of both legs were approximately equal. At equal levels the right-thigh diameter exceeded that of the left by 1.5 cm. The limb lengths were equal. There was no associated motor weakness or sensory disturbance. Digital pressure over the right femoral artery sufficient to obliterate the dorsalis-pedis pulse had no effect on the pulsation or bruit of the mass, nor did it affect the pulse rate, which remained at 70.

The preoperative impression was that the patient was suffering from an active, expanding, pulsating hematoma or "false aneurysm," possibly related to deep epigastric or ovarian-artery injury incurred at the time of surgery 3 months previously. In view of the continuous pain and increasing size of the mass, immediate exploration was advised and accepted.

Under continuous spinal anesthesia a long right-diagonal incision was deepened to open the inguinal canal and was extended upward and laterally into the flank. The deep epigastric vessels, found intact, were ligated and divided at their origin, and the peritoneal pouch was mobilized mesially to expose the iliac vessels as far as their bifurcation. Separate greased umbilical tapes were loosely placed around the common iliac and external iliac arteries for possible emergency use.

A second incision was next made, starting at the right anterior superior iliac spine and running over the pulsating femoral mass, curving downward and medially, to parallel the femoral vessels into the thigh. After their mobilization, a third greased umbilical tape was placed distally around these vessels (Fig. 1).

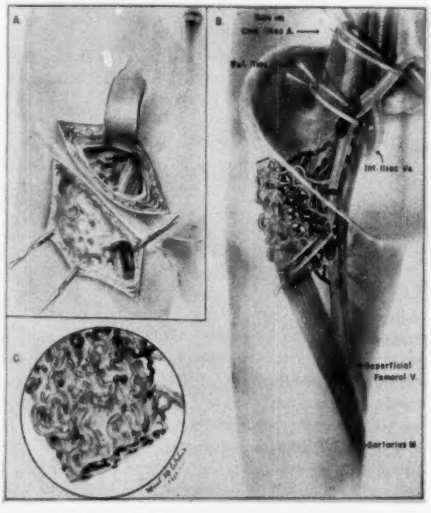

FIGURE 1. *Steps in Operative Technic for Total Excision of Congenital Arteriovenous Fistulation of Lower Limb.*

Temporary occlusion of the common iliac artery stopped all pulsations and activity in the mass. Direct attack was

then made on the mass, which was found to consist of innumerable enormous thin-walled, expansile and tortuous vessels within the sartorius muscle from its origin downward. Some 40 to 50 anomalous vascular tributaries emerged from the external iliac and common femoral arteries and veins. These led laterally into the vascular mass and were individually ligated and divided until the main vessels had been cleared for about 25 cm. from the iliac bifurcation under Poupart's ligament, into the thigh beyond the femoral bifurcation. This accomplished, the vascular mass, which had resembled a nest of writhing earthworms, was quiet and free of blood flow. Auscultation of the iliac bone revealed no bruit. Accordingly, the entire mass was resected en bloc by detaching the sartorius muscle at its origin from the anterior superior iliac spine and transecting it well below the point of its vascular invasion, in mid-thigh. The wounds were then closed in layers, division of the greater saphenous vein being carried out at the saphenofemoral junction as the lower wound was closed. No arterial tributaries approached the saphenous vein. Cotton technic was used throughout. The patient received a single blood transfusion; the entire procedure lasted 3 hours.

The patient was allowed to walk on the first day and was discharged from the hospital on the tenth day, with an apparently normal circulation. No anticoagulants were used. She was seen a year after the operation and was asymptomatic except for persistent postoperative paresthesias of the anterior aspect of the thigh. The anomalous posterior varices remain unchanged.

Pathological diagnosis of the removed specimen was "benign capillary and cavernous hemangioma."

During convalescence the patient pointed to a small silvery scar in her lower-medial right thigh and mentioned a "blood mole" that had bled profusely 10 years previously and that had been treated by cauterization because, as her physician told her, "it had roots."

Two weeks after discharge the patient was given a course of deep roentgen therapy, the total dose amounting to 2000r through a single 15-by-15-cm. portal (200kv-0.5mm. copper 50 cm. distance) to include the site of operative intervention.

Discussion

The aptness of the term "congenital fistulation" is well illustrated in this case of a patient who required separate division and ligation of some 40 communications, over a 25-cm. segment of main vessels. This was approached through separate iliac and thigh incisions.

The case underlines past experiences in which the condition was often not appreciated before operation and emphasizes the wisdom of suspecting the lesion in all cases of varicose veins of the lower extremities—especially unilateral ones appearing suddenly in young subjects at unusual sites. This type of onset is not sufficiently stressed in case reports. The condition should be looked for in young patients with unexplained chronic leg ulcers and in cases of hemihypertrophy of the limbs. In the latter cases differential diagnosis includes ipsilateral phlebitis and wasting disease (such as poliomyelitis) of the contralateral limb. Fresh thromboses, seen in the resected specimen, undoubtedly were the cause of the local stabbing pains that first directed the patient's attention to her pulsatile mass.

Certain surgical principles are illustrated. Operation without tourniquet is advisable, since fistulas may be left unrecognized if blood flow is arrested during dissection. Generous exposures through two incisions, as suggested by Holman,[33] made emergency hemostatic control possible at all times. There must be distal as well as proximal control, since collateral channels may give rise to alarming hemorrhage. If the condition is suspected, preoperative roentgenograms of contiguous bony structures may forewarn the surgeon of their vascular involvement. A sterile stethoscope is a great aid to location of persistent fistulas during operative resection.

En-bloc excision of all involved structures, including main blood vessels if necessary, is required for cure. In our patient it was possible to preserve all important contiguous structures. According to involvement, main arteries may have to be sacrificed. Operation should be performed, as with popliteal-aneurysm resection, with the foot exposed. If collateral channels prove inadequate, bridging vein or arterial grafts will be necessary to preserve the limb. If a fistula is overlooked when a main artery is sacrificed without restoration of main-vessel continuity, gangrene is inevitable. Case reports should include mention of main-channel continuity, since success or failure of resection primarily depends on it. Fortunately, it was possible to preserve such continuity in our case.

Postoperative radiation therapy was prescribed in an endeavor to destroy those endothelial strands presumably remaining and beyond possibility of complete removal. These are the potential shunts that by gradual dilatation, arterialization, elaboration of elastica and phlebectasia[3] in the presence of local arterial-blood-pressure stresses redirected by surgery may become the basis of future pulsatile fistulation. Thus has congenital fistulation been termed the "cancer" of the vascular system. Although it does not undergo mitosis or metastasize, nevertheless it may behave clinically as though it did both, purely as a result of the expansion of old anastomoses and the opening of new anastomoses potentially present from birth. Pratt[31] speaks of a patient with fourteen congenital shunts in one arm who returned one year after treatment with five more. One[32] of the present series was subjected to nine separate operations, with clinical improvement but persistent bruit. Such a possibility must be explained to the patient, lest new developments be construed as recurrence due to faulty technic.

Summary

Congenital arteriovenous shunts, as compared to the traumatic variety, are almost always multiple. Additional potential shunts threaten to open and expand at any time. "Fistulation," therefore, rather than "fistula," seems a more appropriate term. A significant series of 79 published cases of congenital arteriovenous fistulation of the lower extremity is summarized. Among these only 29 were considered operable, only 4 being cured (all by resection) and 13, or nearly 50 per cent, necessitating amputation. Success or failure of resection depends primarily on preservation or reconstruction of main-artery

continuity. A favorable case, successfully managed by total resection, is reported in detail.

References

1. O'Neil, E. E. Congenital arteriovenous fistula. *New Eng. J. Med.* **221**:133-136, 1939.
2. Pemberton, J. deJ., and Saint, J. H. Congenital arteriovenous communications. *Surg., Gynec. & Obst.* **14**:470-483, 1928.
3. Pennoyer, G. P. Symposium on surgical diagnosis: congenital arteriovenous aneurysms or fistulas. *S. Clin. North America* **26**:343-348, 1946.
4. Callander, C. L. Study of arteriovenous fistula with analysis of 447 cases. *Ann. Surg.* **71**:428, 1920.
5. Abramson, P. D. Clinical aspects of arteriovenous fistulae. *Am. J. Surg.* **44**:429-440, 1939.
6. Benchimol, A. S., and Montero, J. B. Fistulas arteriovenosas congénitas. *Prensa méd. argent.* **37**:187-196, 1950.
7. Carson, W. J. Congenital arteriovenous communication. *West. J. Surg.* **44**:283-286, 1936.
8. deTakats, G. Vascular anomalies of extremities. *Surg., Gynec. & Obst.* **55**:227-237, 1932.
9. Gilmour, J., and Bolam, M. Congenital arteriovenous communications with report of two cases. *Brit. J. Surg.* **25**:337-343, 1937.
10. Gross, S. W. Cited by Lewis.[26] *Lancet* **2**:680-686, 1930.
11. Harris, K. E., and Wright, G. P. Case of hemangiectatic hypertrophy of limb and observations upon rate of growth in presence of increased blood supply. *Heart* **15**:141-149, 1930.
12. Hewitt, P. Case of congenital aneurysmal varix. *Lancet* **1**:146, 1867.
13. Horton, B. T. Abnormal arteriovenous communications. *M. Clin. North America* **15**:227-232, 1931.
14. Horton, B. T., and Ghormley, R. K. Congenital arteriovenous fistulas of extremities visualized by arteriograph. *Surg., Gynec. & Obst.* **60**:978-983, 1935.
15. Horton, B. T. Hemihypertrophy of extremities associated with congenital arteriovenous fistula. *J. A. M. A.* **98**:373-379, 1932.
16. Israel. Cited by Lewis.[26]
17. Janes, J. M., and Musgrove, J. E. Effect of arteriovenous fistula on growth of bone. *S. Clin. North America* **30**:1191-1200, 1950.
18. Laskey, N. F. Cirsoid aneurysm, with report of unusual case. *Am. J. Surg.* **20**:128-130, 1933.
19. Perthes. Cited by Lewis.[26]
20. Reid, M. R., and Conway, H. G. Congenital cirsoid aneurysm of leg. *J. A. M. A.* **101**:1391-1393, 1933.
21. Reid, M. R., and McGuire, J. Arteriovenous aneurysms. *Ann. Surg.* **108**:643-693, 1938.
22. Rienhoff, W. F., Jr. Congenital arteriovenous fistula. *J. A. M. A.* **83**:743-750, 1924.
23. Seeger, S. J. Congenital arteriovenous anastomoses. *Surgery* **3**: 264-305, 1938.
24. Stoner, A. P. Injection treatment for varicose veins, with special reference to attending dangers and complications: report of case of congenital arteriovenous fistula. *Am. J. Surg.* **16**:444-450, 1932.
25. Veal, J. R., and McCord, W. M. Congenital abnormal arteriovenous anastomoses of extremities (with special reference to diagnosis by arteriography and by oxygen saturation test). *Arch. Surg.* **33**: 848-866, 1936.
26. Von Eiselsberg. Cited by Lewis.[26]
27. Ward, C. E., and Horton, B. T. Congenital arteriovenous fistulas in children. *J. Pediat.* **16**:746-766, 1940.
28. Wise, W. D., and Lisansky, E. T. Congenital arteriovenous fistula or fistulae: case report. *Ann. Surg.* **108**:701-704, 1938.
29. Dandy, W. E. Venous abnormalities and angiomas of brain. *Arch. Surg.* **17**:190-243, 1928.
30. Lewis, D. Congenital arteriovenous fistulae. *Lancet* **2**:621-628 and 680-686, 1930.
31. Pratt, G. H. Arterial varices: syndrome. *Am. J. Surg.* **77**:456-460, 1949.
32. Reid, M. R. Report of vascular lesions. *Am. J. Surg.* **14**:17-54, 1931.
33. Holman, E. Immediate and late treatment of arteriovenous fistula. *Ann. Surg.* **122**:210-222, 1945.

BIMEDIAL LOBOTOMY*

Its Superiority over the Conventional Approach

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LOBOTOMY investigations at the Boston Psychopathic Hospital during the last two years have centered about a comparative evaluation of three different types of frontal-lobe surgery — bilateral, bimedial and unilateral lobotomy. A pilot study of bimedial and unilateral lobotomy in 1950 by Bockoven and Greenblatt[1] indicated that these two modifications of the standard operation had definite potentialities for improving chronically ill mental patients. The investigations here reported are part of a larger project that over eight years has had two essential aims: to develop an operation that would accomplish the most benefit for the patient with the least personality and brain damage and to illuminate the functions of the frontal lobe.

Operations

All the operations described in this report were performed by Dr. James L. Poppen and his associates from the Neurosurgical Department of the Lahey Clinic. Dr. Poppen utilizes a superior approach, making a bone button the size of a half dollar anterior to the coronal suture. All operative procedures are carried out under direct vision. The plane of section lies just anterior to the ventricle, the caudate nucleus and Areas 13 and 14 in the base of the brain. Dr. Poppen's technic has been described in detail.[2]

Definition of Operations

Bilateral lobotomy consists of sectioning of all the white matter in both frontal lobes in the operative plane. This is the conventional operation.

Bimedial operation consists of sectioning of the white matter only in the medial aspects of the operative plane bilaterally.

Unilateral lobotomy consists of full sectioning of the white matter on either the right or the left side but not on both.

Either bimedial or unilateral lobotomy in anatomic terms involves cutting approximately one-half the fibers sectioned in the conventional full bilateral lobotomy.

Subjects

The report is based on follow-up of 110 chronic mentally ill patients who were the subjects in a consecutive operative series of 125 cases. These

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patients had failed to respond to all procedures, including somatic treatment, psychotherapy and long hospitalization. The age distribution is as follows: fifteen to twenty-four years — 9 cases; twenty-five to thirty-four years — 34 cases; thirty-five to forty-four years — 44 cases; forty-five to fifty-four years — 19 cases; and fifty-five to fifty-nine years — 4 cases. Forty-one were male and 69 female. Ninety-one belonged to the schizophrenic group, of which the majority were diagnosed as either dementia praecox paranoid or dementia praecox catatonic. In this group some 25 were diagnosed as dementia praecox hebephrenic and eight were included under "dementia praecox — other types." Only three were diagnosed as having affective psychoses. Four had chronic severe psychoneurotic conditions, and the others belonged to miscellaneous diagnostic categories.

Most of the patients had been hospitalized between two and ten years. Fifty-five patients, representing 50 per cent of the total, had been hospitalized up to five years; 28, representing 25 per cent of the total, had been hospitalized five to ten years; 27, or 25 per cent of the total, had been hospitalized over ten years. The patients had in general received very intensive treatment prior to their operations. Fifty-four, representing 49 per cent of the total, received electric-shock treatment; 14, or 13 per cent, received electric shock treatment and insulin; 10, or 9 per cent, received electric shock treatment and metrazol; 3, or 3 per cent, received insulin alone; 11, or 10 per cent, had other somatic treatments; and 18, or 16 per cent, received no somatic treatment. Altogether, the group is similar to that reported in previous studies from this hospital except that there were fewer affective states; hence the over-all improvement or recovery rate was somewhat less than that reported in previous communications.

Patients were assigned at random to the different types of operations, thus making three essentially equivalent groups from which valid comparisons could be drawn.

The follow-up period ranged from four to twenty-two months, the majority having been studied twelve months or more after operation. Many were seen repeatedly during the follow-up period, and some forty of the total group became the subject of intensive interdisciplinary investigation by a research team of psychiatrists, sociologists, psychologists and physiologists. The results of these studies will be reported subsequently.

Results

Clinical Outcome

Over-all clinical change was rated as marked, moderate or slight improvement; no improvement; and worse. Marked improvement was defined as complete freedom from abnormal ideas, well organized thinking and behavior and good adjustment in the environment. The majority of patients so rated were in the community functioning on a par with citizens free of mental disease.

Moderate improvement consisted of a partial remission of mental abnormalities with a definitely higher level of adjustment than existed before operation. Delusional ideas were present in many of these patients, but no untoward reaction to these ideas was noted in the social situation.

Slight improvement referred to a reduction of some of the major psychotic symptoms, that is, overactivity, aggression or delusions, but the patient still remained psychotic and usually in the same environment as preoperatively. He was, however, less of a nursing problem and usually happier.

Unimproved cases showed no essential change.

The patients designated as "worse" showed greater disorganization of thinking and behavior, or became unpredictable or impulsive.

Table 1. *Rating of Over-All Clinical Changes after Various Frontal-Lobe Operations in Chronic Mental Disease.*

Operation	Marked Improvement	Moderate Improvement	Slight Improvement	Unimproved	Worse
Bimedial lobotomy (32 cases)	13 (41%)	7 (22%)	8 (24%)	4 (13%)	0
Bilateral lobotomy (36 cases)	8 (22%)	8 (22%)	11 (31%)	8 (22%)	1 (3%)
Unilateral lobotomy (42 cases)	9 (21%)	3 (7%)	13 (31%)	13 (31%)	4 (10%)
Total (110 cases)	30 (27%)	18 (16%)	32 (30%)	25 (23%)	5 (5%)

Table 1 shows the results for the three operative groups. It should be noted that approximately twice as many of the bimedial cases (41 per cent) were considered markedly improved as either the bilateral (22 per cent) or unilateral (21 per cent). The fact that patients may respond to any one of these operations is most significant. Heretofore, it has not been generally believed that the unilateral operation is capable of effecting significant improvement in many chronically ill mental cases. This finding does much to discredit the hypothesis that isolation of one frontal lobe has little or no effect on the organism.

Combining cases rated as marked and moderately improved, — which is justifiable, for these patients were improved beyond a doubt, — the figures were: bimedial lobotomy, 63 per cent; bilateral lobotomy, 44 per cent; and unilateral lobotomy, 28 per cent. Again bimedial lobotomy leads all the rest. The

total trend toward improvement (considering all categories) is greatest for bimedial lobotomy and least for the unilateral lobotomy cases. It may be significant that 4 cases (10 per cent) given unilateral lobotomy, 1 case (3 per cent) of bilateral lobotomy and no cases of bimedial lobotomy were judged worse after operation. Although unilateral lobotomy is effective in producing improvement in a significant, though relatively small, proportion of chronic psychotic cases, the possibility of producing increased disorganization in some patients must be recognized. This finding, too, is contrary to the notion that unilateral lobotomy produces no significant change.

Results by Diagnostic Categories

An analysis of improvement in relation to diagnostic categories revealed that improvement may be achieved in any diagnostic subgroup with the different operations. Three suggestions arose in this analysis which may be mentioned — first, that bimedial lobotomy may be of particular value in

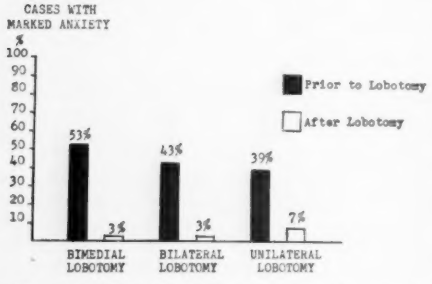

FIGURE 1. *Effect of Lobotomy in Patients with Anxiety.*

catatonic patients; secondly, that the unilateral approach may be of special value in the paranoid state; and thirdly, that bilateral operation may be necessary to achieve any improvement at all in hebephrenic cases. These are in the nature of trends in the data and cannot be regarded as established until a much larger series of cases is studied.

Effect of the Operation on Important Clinical Variables

Anxiety. Figure 1 shows the effect of the several operations on anxiety. Anxiety was defined as heightened unpleasant state of tension or apprehension accompanied by somatic signs and including often specific fears. Anxiety was rated either as minimal, moderate or severe. For purposes of brevity Figure 1 refers only to cases with *marked* anxiety. Although all three operations were effective in reducing anxiety, the clinical improvement in many important respects did not necessarily parallel the anxiety reduction.

Disorganization of thinking. The effect of the lobotomy on disorganization of thinking (Fig. 2) is extremely important, for dissociation, incoherence of thought and lack of congruence between affect and idea have classically been considered the nuclear phenomena in schizophrenia by Bleuler and others. Disorganization of thinking was rated as

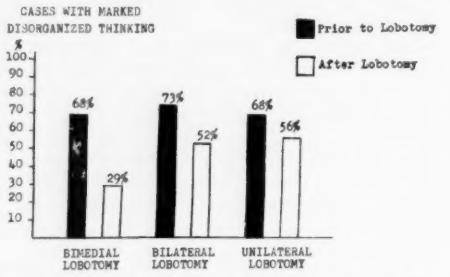

FIGURE 2. *Effect of Lobotomy in Patients with Marked Disorganization of Thinking.*

marked, moderate or minimal. The graph (for purposes of brevity) refers only to cases with marked disorganization of thinking. The figure shows that the reduction of disorganization of thinking effected by bimedial operation is greater than for bilateral or unilateral. This is consistent with the clinical impression of psychiatrists of the Boston Psychopathic Hospital who have been in daily contact with these cases. Rorschach studies in these patients indicate that bimedial operation is followed by less constriction in thinking and much less diminution of phantasy and imaginative processes than follows the other two operative procedures.

Initiative. Initiative was also rated as good, fair or poor. A patient was rated as "good" if he in-

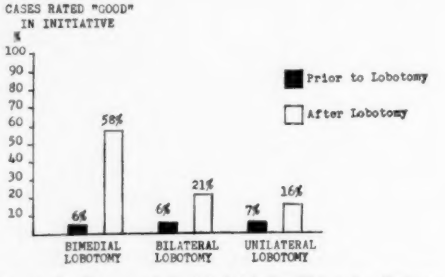

FIGURE 3. *Degrees of Social Initiative Shown by Patients before and after Lobotomy.*

itiated interaction with others, showed spontaneity and sustained interest either in ward or home and was productive. Superiority in initiative was noted in bimedial cases after operation as compared with the other types of operation (Fig. 3). The fact

that all these groups were rated similarly in initiative before operation strengthens the significance of the difference found. In addition to ratings of initiative, ratings of emotional warmth and responsiveness were also made. They suggest that there is more warmth and appropriate emotional reaction in the bimedial group.

The observations above, particularly of initiative and emotional response, are particularly pertinent to the question of "blunting," which has been raised so often as an argument against full bilateral lobotomy and has been one of the chief motives for investigating more restricted operations. Most authors who use the term "blunting" have not been very precise concerning its meaning; however, one gains the impression that they refer to indifference, apathy, shallowness of affect, lack of emotional response or low initiative. It appears that precisely in this area lies the superiority of the bimedial operation.*

Untoward effects. Significant untoward effects were convulsive seizures and enuresis. Convulsive seizures occurred altogether in 18 patients, or 16 per cent of the total group studied.† Eight of the cases with seizures were in the bilateral group, 7 in the bimedial group and 3 in the unilateral group. Cortical damage almost of necessity is greater in bilateral operations than in unilateral operations. Most of the patients with convulsions suffered occasional or few seizures, responded to medication and were readily kept under control.

Enuresis occurred in 6 cases of the bilateral series, 7 of the bimedial series and 5 of the unilateral series. Two patients soiled at some time during the follow-up period — one a bilateral case and one a bimedial case.

Both seizures and wetting are significant complications, not to be underestimated and always to be weighed carefully in considering the advisability of frontal-lobe surgery in chronic mental disease. However, the evidence to date suggests that the danger of these complications *is not greater* for the bimedial than for the conventional bilateral operation. It may be less for unilateral operation.

*Although it is not within the scope of this paper, nevertheless it is pertinent that independent investigations by three social workers at the Boston Psychopathic Hospital (Sanford J. Freedman, Julian B. Carrick and Gladys Madoff) who directed their attention primarily to changes produced by operations on level of social adjustment also indicated the superiority of bimedial operation.

†This represents an increase over the 12 per cent reported previously in a one-to-four-year follow-up of 205 cases of bilateral lobotomy[1]; the factors related to this increase are being investigated.

Discussion

These investigations go far toward establishing the following conclusions: that it is not necessary to perform complete bilateral sections of white matter in the coronal plane in order to achieve therapeutic results; that operations that sever roughly one-half that amount of white matter are effective in improving patients; that bilateral section of the medial frontal fibers is especially effective in obtaining reduction in anxiety, decrease in disorganization, increase in initiative, preservation of emotional response and greater over-all improvement rate; and that, contrary to general belief, unilateral operations may be highly effective in some patients (the distinguishing characteristics of this group, however, have not as yet been defined).

Summary

Bimedial lobotomy is superior to bilateral lobotomy and unilateral lobotomy in that the over-all improvement rate is greater; the beneficial effect on dissociation of thought is greater; the beneficial effect on initiative is greater; and disorganization and impulsive and unpredictable behavior are lessened.

The reduction in anxiety following bimedial lobotomy is as great as that following bilateral lobotomy and probably greater than that following unilateral lobotomy.

Convulsive seizures and enuresis are more frequent after bilateral and bimedial than after unilateral lobotomy.

References

1. Bockoven, J. S., and Greenblatt, M. Results of unilateral and bimedial lobotomy. In *Studies in Lobotomy*. Edited by M. Greenblatt, R. Arnst and H. C. Solomon. New York: Grune and Stratton, 1950. Pp. 246-253.
2. Poppen, J. L. Technic and complications of standard prefrontal lobotomy. *Ibid.* Pp. 67-74.

MEDICAL PROGRESS

ALLERGY TO DRUGS*

EDWARD A. CARR, JR., M.D.†

PHILADELPHIA

THE seventeenth century must have been the nadir of therapeutics, if we can believe Molière, for one of his characters remarks: "Almost everyone dies of the remedy, not the malady." Fortunately, since then many drugs that were poisonous to the majority of patients have been abandoned, and, more recently, the adoption of preliminary toxicity tests on animals has done much to prevent new examples from reaching the clinic. In the past few decades, however, as advances in synthetic chemistry have made increasing numbers of new drugs available, one type of poisoning, — allergy to drugs, — has become more and more important. This review will consider the definition of allergic reactions as opposed to other types of drug reactions; the mechanism of allergy to drugs; certain manifestations of allergy that are provoked exclusively or most commonly by drugs; certain drugs that deserve special attention as allergens; and some aspects of diagnosis, prevention and treatment of allergic reactions.

DEFINITION

Allergy is "any specifically acquired alteration in the capacity of living tissue to react. This alteration in capacity to react results from exposure to an exciting agent and is manifested upon re-exposure to the same or to an immunologically related agent."[1] Three features of this definition deserve comment.

First, the alteration is specific. If one repeatedly injects into the subcutaneous tissue of an animal a compound that causes local inflammation and that when absorbed also damages the liver, the first injection may fail to be absorbed rapidly enough to cause liver damage, whereas the second, injected at the same site, may cause liver damage because the subcutaneous inflammation that is now present promotes absorption. The animal is not allergic, since it is obvious that other injected poisons of entirely different chemical structures would now similarly show increased absorption and systemic effect.

Secondly, the concept, as originally proposed by von Pirquet and as here defined, includes those reactions commonly termed "immune" as well as those commonly termed "allergic," and it must be admitted at once that there is no universal and sharp distinction between the two. When an animal possessing antibodies to a bacterial toxin as a result of previous exposure is re-exposed to the same toxin, a reaction occurs between the toxin and the antibodies, and the characteristic symptoms of poisoning by that toxin are avoided. This primary union between antigen and antibody, which makes the animal hyporeactive and protects him, is conveniently termed an immune reaction.

The experiment can, however, be designed so that the union between antigen and antibody starts a train of secondary reactions, — anaphylactic shock, — which is not characteristic of the toxin itself; any one of many substances can be used to sensitize and then shock the animal, the final picture being the same in all cases. It is such secondary and detrimental hyperreactions, of which anaphylactic shock is only one example, that will be considered as allergic in the narrower sense and as such discussed here. Although it is convenient to think of reactions of this type as being secondary, detrimental hyperreactions, it must be remembered that in most allergic reactions to drugs one cannot even demonstrate the existence of an antibody and cannot speak with certainty of primary versus secondary reactions, that the distinction between protective and detrimental is a philosophical one and that the terms "hyperreaction" and "hyporeaction" presuppose a far greater knowledge of the chemistry of the tissues than we have at present.

Thirdly, hypersensitivity not acquired through previous contact is not allergy. If a dose of 600 mg. of acetylsalicylic acid is given to each of a large series of patients, it is likely that a few will experience considerable tinnitus on first as well as subsequent exposure to the drug. Such patients are hypersensitive but not allergic. In contrast, some patients tolerate initial exposure to acetylsalicylic acid but on re-exposure develop attacks of bronchial asthma. They have become allergic to the drug. Furthermore, although all patients are probably capable of manifesting tinnitus after acetylsalicylic acid if the dose is large enough the ability to react with an asthmatic attack is limited to a few, regardless of the dosage used. However, allergic reactions are not always limited to the minority. It has been found[2] that about three fourths of the population can be made to develop poison-ivy dermatitis. This is clearly an allergy, for studies have shown that Eskimos[3] and infants[4], who have had no natural exposure to the plant, do not develop dermatitis when experimentally exposed to it but may develop dermatitis on re-exposure. In his experiments with

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primrose, Bloch[5] was able to sensitize all his subjects.

Deciding whether a given reaction to a drug is allergic or not is by no means academic quibbling. It will obviously remain impossible to investigate in detail the mechanism, prevention, treatment and so forth of each instance of allergy to drugs, and progress in this field will continue to depend on the development of general principles from investigation of reactions to a few substances. Such principles, however, cannot be expected to apply to reactions that have nothing to do with allergy in the first place.

Mechanism

In considering the mechanism by which allergy to drugs arises, we must distinguish between drugs like insulin, which are proteins, and the majority of drugs, which are relatively simple substances. Proteins, as well as certain polysaccharides and lipocarbohydrate complexes of high molecular weight, are complete antigens,[6] that is, they can by themselves produce the allergic state and elicit the reactions characteristic of that state. Allergy to protein drugs is not fundamentally different from allergy to any other protein and will not be further considered in this review. The early work on allergy to protein drugs, up to 1940, has been reviewed by Harten and Walzer.[7]

Allergy to relatively simple chemical substances, however, presents quite another problem, as these substances are by themselves incapable of sensitizing. The remarkable and illuminating series of experiments conducted by Landsteiner, Chase and their associates[8-15] strongly suggests that such substances combine with body proteins to form conjugates that then act as antigens. The hapten, — that is, the simple substance, — confers specificity on the conjugate; hence the allergy is directed against the hapten and not against the protein. It is desirable to review briefly the experiments supporting this concept. They will be seen to have clinical implications concerning the risk of sensitization when the skin is the route by which exposure to a drug occurs, the risk of producing allergic symptoms when a drug chemically similar to the original sensitizing drug is substituted for the latter, the difficulty in using, for diagnostic purposes, technics that depend on the presence of circulating antibody, and the possibility of developing specific prophylaxis or treatment.

The history of events preceding Landsteiner's studies has been reviewed by Cormia[16] and Landsteiner.[9] In 1907 Wolff-Eisner advanced the hypothesis that simple substances could conjugate with proteins in vivo to form antigens. In 1911 Cash experimentally produced human allergy to a simple chemical substance. In 1912 Swift produced anaphylaxis in guinea pigs, using as antigen a mixture of neutralized arsphenamine and guinea-pig serum. Landsteiner and his associates showed that antibodies against a simple compound, arsanilic acid, could be produced by chemically linking the arsanilic acid to a protein in vitro and injecting the conjugate into rabbits. The antibodies formed by the rabbit were specifically directed against the hapten, arsanilic acid, as shown by the fact that the rabbit serum gave positive precipitin tests when a conjugate of arsanilic acid with the original protein or a conjugate of arsanilic acid with a different protein was used in the test, but not when a conjugate of the original protein with some other hapten unrelated to arsanilic acid was used. Furthermore, although the arsanilic acid itself, not conjugated with any protein, did not give a positive precipitin test, one could still show that the unconjugated arsanilic acid was capable of uniting with the antibodies in the rabbit serum. To show this, arsanilic acid was added to the rabbit serum and an arsanilic acid-protein conjugate was then added. Precipitation did *not* occur; the unconjugated hapten had combined with the antibody and inhibited the precipitation that would otherwise have occurred when the conjugate was added. Here again the reaction was specific for arsanilic acid, other unrelated haptens failing to cause inhibition.

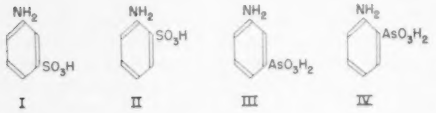
In other experiments antiserums were produced against hapten-protein conjugates, but the precipitin tests were carried out differently. Instead of linking the hapten with a protein, Landsteiner linked the hapten with another compound to form an azodye. This azodye, incorporating the hapten, then gave positive precipitin reactions with the specific antiserum. Here again the unconjugated hapten caused specific inhibition. In addition, the azodyes, when injected into sensitized animals, produced anaphylactic shock. Under proper conditions the azodyes were also capable of desensitizing the animals.

Although these experiments of necessity involved the use of synthetic conjugates, there is evidence that conjugation occurs in vivo. In a group of closely related compounds of the halobenzene and nitrobenzene series, the ability of each compound to sensitize the skin was found to be correlated with its ability to react with aniline in vitro. Reactivity with aniline was assumed to be a measure of reactivity with similar chemical groups in protein molecules. This assumption led to the prediction that benzyl and acyl chlorides would be potent sensitizing agents — a prediction shown by subsequent experiments to be correct.

Cross reactions, that is, reactions to compounds other than the original sensitizer, have been studied with the technics described above. From such experiments it can be stated, — and this is a most important principle, — that cross reactions usually "make sense" chemically; that is, they occur most often between chemically similar compounds. For example, when the sensitizing hapten was *m*-amino-

sulfonic acid (I), cross reactions occurred with (II) and (III) but not with (IV), which is chemically the least similar to (I). Individuals differed, however, in the pattern of cross reactions shown by their serums.

Although the haptens used in most of these experiments were not substances of pharmacologic importance, familiar drugs have been shown to



behave similarly. Although differing widely in details of technic, the experiments of Mulinos[17] with antipyrine-protein conjugates and of Wedum[18] with sulfonamide-protein conjugates gave results consistent with this principle.

Most of these experiments have dealt with the "immediate" or "urticarial" type of allergic response, in which anaphylaxis is a typical occurrence, circulating antibodies are usually demonstrable and temporary desensitization is often possible. Most clinical allergies to drugs, however, are of the "delayed" or "tuberculin" type. The skin is the commonest site of these reactions, circulating antibodies are not usually demonstrable and desensitization is not often successful. But experiments that bridge the gap between the two types of allergic response were also performed by Landsteiner and Chase and their co-workers. When a guinea pig was made allergic to picryl chloride by repeated intracutaneous injections, subsequent contact testing of the skin with the sensitizing agent produced an eruption, whereas intravenous injection of a protein conjugate of the picryl chloride led to anaphylaxis. In other experiments of this type it was found that the anaphylactic type of allergy could be abolished by a desensitization technic employing the conjugate, whereas the skin allergy could not be abolished by any technic. If no other evidence were available, this work might suggest that when the skin is presented with the hapten and presumably allowed to make its own conjugate the result is the "delayed" type of allergy, whereas the introduction of a preformed conjugate leads to the "immediate" type of allergy. However, other experiments have shown that preformed conjugates can also sensitize the skin under the proper conditions. When picryl chloride was coupled with homologous red-cell stromas and injected intraperitoneally into guinea pigs, the latter developed both the "delayed" contact type of skin allergy, evoked by testing the skin with the hapten, and the "immediate" anaphylactic type of allergy, evoked by intravenous injection of a conjugate of the hapten with serum protein. Thus, although the skin is the route of choice if one wishes to produce contact dermatitis, it is not an obligatory route.

Although circulating extracellular antibody is notably absent in the "delayed" type of allergy, cells of the allergic animal must contain antibody, — at least in some instances, — for the washed, living white cells of a peritoneal exudate of such an animal have passively transferred this type of allergy to another animal.[19]

Finally, it should be noted that many of the substances used to sensitize the skin of laboratory animals also sensitize human skin. The importance of chemical similarity in cross reactions has also been shown in human beings.[20] Skepticism concerning the applicability of animal experimentation to problems of human allergy to drugs should be tempered by the realization that in the field of allergy to proteins a remarkable similarity between experimental animals and human beings has already been shown. Most of the important reactions studied in laboratory animals, such as the Arthus phenomenon, acute and delayed anaphylactic shock, passive sensitization and reversed anaphylaxis, have been produced in man.[21]

Manifestations

The manifestations of allergy to drugs include: reactions that are also seen in allergy to proteins, such as asthma, conjunctivitis, urticaria, angioneurotic edema, the syndrome of serum sickness and periarteritis nodosa; dermatitis; and reactions that are not characteristic of allergy to proteins, such as bone-marrow depression, fever that may be unaccompanied by other manifestations of allergy and hepatitis.

Asthma, *conjunctivitis*, *urticaria*, and *angioneurotic edema* are familiar manifestations that will be briefly discussed later in connection with Table 2. Rich[22-25] found fresh lesions of *periarteritis nodosa* in patients dying during *serum sickness* and was able to produce periarteritis nodosa in rabbits by sensitizing them to foreign serum. Other workers[26, 27] not only confirmed this but were able to prevent the development of periarteritis in serum-treated rabbits by suppressing antibody formation with the aid of nitrogen mustard. A syndrome similar to serum sickness has been reported after administration of sulfonamides,[21] penicillin[28] and iodine.[25] The finding of fresh lesions of periarteritis nodosa in a patient who had received sulfathiazole but no serum was thus of great interest. Periarteritis has also been reported to follow iodine,[29] aspirin,[28] dilantin,[28] thiouracil,[30] propylthiouracil[31] and methylthiouracil.[32] It is possible that the granulomas and focal necroses described in the tissues of patients who had received sulfonamides[33-35] represent the same reaction. In some cases in which periarteritis has been ascribed to the use of a drug, the evidence has merely con-

sisted of the fact that the patient received the drug in question and was later found to have periarteritis. The case of periarteritis associated with propylthiouracil treatment cited above, however, offers strong evidence that the lesions were due to allergy to the drug. The patient tolerated initial exposure to propylthiouracil without signs of periarteritis. Readministration several weeks later led to the development of fever, diarrhea, weakness, mental confusion and pareses suggesting cerebral vascular lesions. The patient improved when the drug was stopped, and readministration led to prompt and clear-cut exacerbations on two separate occasions. Autopsy showed periarteritis.

The development of the syndrome of fever, lymphadenopathy, arthralgia, and urticaria several days after initial administration of a drug must therefore cause some concern. This point should not be exaggerated, however. Classical serum sickness has been known for many years, and its benign nature in the majority of patients is now well established. Although patients who developed the syndrome after the use of the newer drugs have not been followed for a long enough time to permit definite conclusions, it is encouraging to note that no minor epidemics of periarteritis have been provoked to date. On the other hand, the absence of the serum-sickness syndrome is no guarantee that periarteritis may not follow the use of a drug, as the reported cases have already shown.

Dermatitis due to allergy to ingested proteins has been much discussed and is an important pediatric problem. The statement made several years ago by Hill[36] is still an admirable expression of the status of the problem: "I have seen nothing in the literature, including my own contributions, which leads me to believe that anyone really understands infantile eczema." As a result of the studies previously mentioned, allergic dermatitis due to contact with simple chemical substances is better understood. Nevertheless, it must be admitted that animal experimentation has failed in one important respect. In clinical skin allergy to drugs, the route of exposure is often not the skin. Patients may be sensitized and reactions elicited through any of the usual routes of administration, including the oral, but attempts to sensitize laboratory animals via the oral route have been regularly unsuccessful. It has been observed, however, that patients who develop contact dermatitis (that is, who have their skin sensitized by direct exposure) may later suffer a prompt exacerbation of the skin lesions when the drug is given by mouth, and vice versa.[37, 38]

The allergic dermatitis produced by some ingested drugs, such as antipyrine, may be sharply localized to certain small skin areas, and readministration may repeatedly provoke an eruption only in these areas. The sites of such fixed eruptions may vary from patient to patient. It was formerly stated that fixed eruptions were due only to drugs, but a few cases contradicting this are on record, including one in which tomatoes were shown to be the cause.[37] It is highly probable that simple chemical substances that are not drugs in the usual sense could be found to produce fixed eruptions — or, indeed, any other manifestation of allergy to drugs in human beings, if sufficient opportunity for large-scale exposure existed. Sievers[39] produced fixed urticarial sensitization to sulfobromophthalein (bromsulfalein) by paravascular injection.

Attempts to investigate fixed eruptions by skin transplantation have yielded contradictory results[40, 41] and have not answered the question "Why does an ingested substance, which has presumably been carried by the circulation to all areas of the skin, sensitize only one area?" The complementary question is: "In contact dermatitis, how does a substance applied to one area of the skin sensitize the entire skin?" The results of experiments with skin islands strongly support the hypothesis that the substance, on coming in contact with the skin, is modified in some way during the succeeding few hours and that this modified substance, — perhaps the hapten conjugated to protein, — is absorbed. It is not known whether the antigen is then distributed to all areas of the skin or whether an antibody eventually produced is the substance that is distributed. It is probable that a small concentration of antigen remains at the original site of application, as the first indication of sensitization at the end of the incubation period is often a "flare-up," that is, a *spontaneous* eruption at this site.[2] This subject, as well as evidence bearing on the exact route of distribution, has been reviewed by Rostenberg.[42]

Although we are concerned here with allergic dermatitis and not with primary irritation of the skin, it has been observed that substances that are primary irritants are often effective sensitizers. The role of irritation in increasing the incidence of experimental sensitization has been stressed by Chase.[43] This suggests that patients treated with topical applications of drugs for inflammatory skin lesions run a greater risk of becoming sensitized by virtue of the very fact that they have such lesions. Sulzberger and Rostenberg[44] demonstrated increased susceptibility to sensitization by local application of simple compounds in patients who already had allergic contact dermatitis from other compounds, but these results are not necessarily applicable to patients suffering from nonallergic dermatitis. Underwood and Gaul[45] compared the results of exposure to merthiolate in 187 patients with skin diseases and 88 surgical patients. Patch tests revealed that 66 of the former and none of the latter had become sensitized. The factor of possible increased number of applications in the patients with skin disease cannot be dismissed, however.

The effectiveness of the skin as a sensitizing route and the possible increased incidence of sen-

sitization in patients with pre-existing dermatitis suggest that topical treatment of dermatitis with potent sensitizing agents, when such drugs could equally well be given by mouth or by injection, is poor practice. Clinical experience with the sulfonamides and penicillin has apparently well substantiated these theoretical considerations. Conclusive proof would require that two comparable groups of patients with skin disease receive equally effective treatment, one group systemically and one group topically. But in the absence of such a conclusive study, Sulzberger's[46] demonstration that he could sensitize the skin of 19 per cent of 259 volunteers with sulfonamide ointment is impressive. An artificial burn was the site of application. It is not surprising that Gottschaik and Weiss,[47] using volunteers with no lesions, obtained a much lower incidence of sensitization. There are numerous reports of sensitization to sulfonamide ointments in actual dermatologic practices.[48, 49]

Locally applied penicillin is also a serious sensitizing agent.[50, 51] Comparing local with systemic treatment of apparently equal effectiveness, Hopkins and Lawrence[51] stated that they found a higher incidence of sensitization with the former, but more precise figures would be desirable. The previously mentioned occurrence of reactions on systemic readministration to patients previously sensitized via the skin is an important and disturbing feature of these reports. The seemingly innocuous jar of penicillin or sulfonamide ointment has become the dermatologist's cask of Amontillado.

Sensitization of the skin is by no means synonymous with sensitization of mucous membranes,[37, 52] and the risk of receiving a given drug by inhalation of an aerosol, for example, will have to be separately evaluated. Ophthalmologists, however, are well advised to avoid, whenever possible, application to the conjunctiva of drugs known to be potent skin sensitizers, as such applications almost invariably provide adequate skin exposure.

The discussion thus far has recognized only two classes of allergic dermatitis due to drugs, contact dermatitis and all others. Experienced dermatologists[38] state that certain skin lesions, such as erythema nodosum, definitely tend to be characteristic of certain drugs, although there are no invariable rules. It may not at first seem surprising that different causes should produce different clinical pictures, but a consideration of other types of allergy will show that it is really startling for one organ, admittedly a complex one, in one species to show variations in what appears to be fundamentally one allergic reaction, the variations being conditioned by the antigen. From the clinical standpoint variations in *severity* are important. The experience of Hopkins and Lawrence led them to consider penicillin a more frequent sensitizer of the skin than sulfonamides on local application, but they found the latter to produce a more severe dermatitis.

Exfoliative dermatitis, with its frequently fatal outcome, is the most serious skin lesion attributable to drugs. The best evidence for the allergic nature of this lesion comes from experience with arsenicals. One patient developing exfoliative dermatitis after sixteen days of neoarsphenamine therapy recovered in fifty-three days, the neoarsphenamine having been stopped at the onset of the disease. Nineteen months later he promptly developed exfoliative dermatitis again on administration of one dose of neoarsphenamine not larger than that which he had tolerated in the first days of treatment.[53] Of 10 patients developing "exudative or crustaceous (lesions), necessitating hospitalization" on neoarsphenamine treatment, 5 developed the same lesions again when a dose of 5 mg. of oxophenarsine hydrochloride (mapharsen) was readministered to all several months later.[54] There are convincing reports of exfoliative dermatitis caused by allergy to quinidine,[55] to potassium thiocyanate[56] and to tincture of iodine painted on the skin.[57]

A large number of other drugs have been reported as causes of exfoliative dermatitis. In the preparation of this review the following have been noted: acetylglycarsenobenzene,[58] arsphenamine,[59] bismarsen,[60] codeine,[61] diethylstilbestrol,[62] dinitrophenol,[63] dilantin,[64] at least 9 different gold-containing preparations,[65] oxophenarsine hydrochloride (mapharsen),[66] mesantoin,[67] nirvanol,[68] penicillin,[69] phenobarbital,[70] quinacrine,[71] silver arsphenamine,[60] sobisminol,[72] streptomycin,[73] sulfadiazine,[74] sulfamerazine,[75] sulfapyridine,[76] sulfarsphenamine,[59] sulfathiazole,[77] trimethadione (tridione)[78] and tryparsamide.[60] This brief list is undoubtedly incomplete. It refers only to cases in which exfoliative dermatitis developed during or shortly after the use of the drug and in which no other probable cause existed. These drugs are therefore only presumptive causes.

Depression of the bone marrow by certain simple chemical compounds, such as benzol, is certainly not on an allergic basis. But agranulocytosis due to aminopyrine[79, 80] and thrombocytopenic purpura due to neoarsphenamine,[81-83] quinine,[84] quinidine,[85] Sedormid[86] and potassium iodide[87] have been shown to fulfill the criteria of allergy. The authors' vivid description[82] of the almost catastrophic events that followed readministration of neoarsphenamine emphasizes the hazards of this type of investigation. Animal studies are at present of little avail, since allergic agranulocytosis has not been produced in laboratory animals and the only allergic thrombocytopenia produced in them has been due to egg white[88] rather than to a simple compound. Nevertheless, it is very probable that the bone-marrow depression caused by certain other drugs, notably the sulfonamides and the thiouracil group, is allergic in nature. With the possible exception of a few cases,[89] allergic depression of the bone marrow in man is due to simple compounds and not to proteins.

In Table 1 depression of the bone marrow has been classified as agranulocytosis, thrombocytopenic purpura or aplastic anemia. Agranulocytosis is here defined as a count of not more than 200 neutrophils per cu. mm. of blood; thrombocytopenic purpura is here defined as a count of not more than 100,000 platelets per cu. mm. of blood or the complete absence of platelets in the blood smear, associated, in either case, with clinical evidence of hemorrhage; aplastic anemia is here defined as agranulocytosis with thrombocytopenic purpura with evidence of depression of erythropoiesis. The separation into three distinct classes has clinical significance, but intermediates occur. The definitions are admittedly arbitrary.

Acute hemolytic anemia occurring during the first few days of sulfanilamide therapy is probably not allergic in nature but simply represents an extreme example of a process that occurs to some degree in most patients and is independent of previous exposure.[125] In 54 patients treated with sulfanilamide, Townsend and Mulcahy[126] found a mean decrease in hemoglobin of 12 "points" with a spread of from none to 43 "points," the latter being diagnosed as acute hemolytic anemia.

Fever due to drugs and not accompanied by other obvious manifestations such as skin eruptions, — "drug fever," — is an important clinical entity, as it is often a diagnostic problem, but one might expect its mechanism to be basically the same as

TABLE 1.

DRUGS* PROBABLY† CAUSING BONE-MARROW DEPRESSION IN MAN

Agranulocytosis†
- Aminopyrine[78]
- Arsphenamine[80]
- Dinitrophenol[91]
- Gantrisin[92]
- Gold sodium thiosulfate[63]
- Lopion (Sodium -3-allylgoldthiourea-l-formic acid)[100]
- Methaphenilene (Diatrin)[94]
- Methylthiouracil[98]
- Neoarsphenamine[96]
- Nirvanol[97]
- Oxophenarsine Hydrochloride (Mapharsen)[85]
- Prea don[88]
- Propylthiouracil[110]
- R. P. 2339[101]
- Silver arsphenamine[102]‡
- Sulfadiazine[118]
- Sulfamethylthiazole[104]
- Sulfanilamide[105]
- Sulfapyridine[106]
- Sulfarsphenamine[107]
- Sulfathiazole[108]
- Thiouracil[109]
- Trimethadione (Tridione)[111]
- Tripelennamine (Pyribenzamine)[1111]

Thrombocytopenic Purpura†
- Aurothioglucose (Solganal)[62]
- Bismarsen[62]
- Gold calcium keratinate[63]
- Gold sodium thiomalate[63]
- Gold sodium thiosulfate[64]
- Iodine, Tincture of[115]
- Neoarsphenamine[81]
- Nirvanol[98]
- Potassium Iodide[87]
- Quinine[86]
- Quinidine[83]
- Sedormid[84]
- Silver arsphenamine[102]‡
- Sulfadiazine[118]
- Sulfapyridine[114]
- Sulfarsphenamine[113]
- Sulfathiazole[115]
- Thiouracil[109]
- Thiourea[117]
- Triphal (sodium gold mercaptobenzimidazole carbonic acid)[65]

Aplastic Anemia†
- Aurothioglucose (Solganal)[118]
- Dexedrine[113]
- Mesantoin[120]
- Oxophenarsine Hydrochloride(Mapharsen)[121]
- Sulfarsphenamine[122]
- Sulfathiazole[123]
- Trimethadione (Tridione)[124]

*Exclusive of those such as radioactive elements, which depress through a clearly nonallergic mechanism.
†Discussed in text.
‡Agranulocytosis and thrombocytopenic purpura occurred simultaneously without depression of erythropoiesis.

TABLE 2.

DRUGS* REASONABLY WELL† ESTABLISHED AS CAUSES OF CERTAIN ALLERGIC REACTIONS IN MAN

Urticaria
- Acetylsalicylic Acid[128]
- Arsphenamine[129]
- Aureomycin[140]
- Cinchophen[133]
- Dinitrophenol[91]
- Estradiol[7]
- Mercurophylline (Mercuzanthin)[142]
- Neoarsphenamine[82]
- Phenolphthalein[143]
- Penicillin[144]
- Streptomycin[145]
- Sulfobromophthalein (Bromsulfalein)[89]

Angioneurotic Edema
- Aureomycin[146]
- Dinitrophenol[91]
- Penicillin[147]
- Sulfapyridine[155]

Asthma
- Acetylsalicylic Acid[149]
- Meralluride (Mercuhydrin)[150]
- Procaine[151]
- Streptomycin[145]
- Sulfadiazine[152]
- Sulfathiazole[155]

Dermatitis (not contact)
- Antipyrine[134]
- Aureomycin[140]
- Dilantin[144]
- Dinitrophenol[91]
- Neocinophen[135]
- Nirvanol[156]
- Penicillin[147]
- Phenobarbital[158]
- Phenolphthalein[159]
- Potassium iodide[160]
- Potassium thiocyanate[161]
- Quinidine[83]
- Streptomycin[145]
- Sulfadiazine[155]
- Sulfanilamide[163]
- Sulfapyridine[165]
- Sulfathiazole[168]
- Thiouracil[166]
- Tripelennamine (Pyribenzamine)[155]
- Undecylenic Acid[155]

Dermatitis (contact)
- Antazoline (Antistine)[167]
- Butamben picrate (Butesin picrate)[163]
- Cod Liver Oil[169]
- Dimercaprol (BAL)[170]
- Dionine[171]
- Intracaine[172]
- Iodine, Tincture of[17]
- Larocaine[173]
- Merthiolate[174]
- Morphine[175]
- Neoarsphenamine[176]
- Nitrofurazone (Furacin)[177]
- Nupercaine[178]
- Opium[179]
- Penicillin[180]
- Phenolphthalein[181]
- Procaine[182]
- Streptomycin[183]
- Sulfadiazine[47]
- Sulfathiazole[184]
- Tetracaine (Pontocaine)[185]
- Thephorin[186]
- Tripelennamine (Pyribenzamine)[187]
- Tyrothricin[188]

Fever without Other Allergic Manifestations
- Arsphenamine[189]
- Neoarsphenamine[139]
- Quinidine[189]
- Streptomycin[78]
- Sulfadiazine[195]
- Sulfaguanidine[191]
- Sulfapyridine[192]
- Sulfathiazole[193]
- Thiouracil[198]

*Exclusive of proteins and gums.
†Discussed in text.

that of fever associated with other obvious manifestations, as intermediate forms occur. Several drugs have been shown to cause fever on an allergic basis, the most careful studies having been done with the sulfonamides.[127-133]

Liver damage occurring during the administration of many drugs cannot be said to be on an allergic basis.[134] Sugg,[135] however, has described patients with acquired hypersensitivity to cinchophen manifested by liver damage; it is not certain that this hypersensitivity was specific — that is, that the liver was not thereafter more susceptible to damage by a variety of unrelated drugs. Fitzgibbon and Silver[136] reported a case of skin eruption and liver damage associated with sulfonamide therapy; here again specificity was not shown. Animal studies have shown that sulfonamides can damage the liver and have not indicated an allergic basis.[137]

Of the reactions mentioned above, angioneurotic edema, asthma, urticaria, dermatitis from systemic administration of a drug, contact dermatitis and "drug fever" are those for which clear-cut evidence of recurrence on readministration of the drug is likely to be obtained in human beings. The cases that have been encountered in the preparation of this review are listed in Table 2. This list covers principally the decade 1940–1950 and is undoubtedly incomplete. In each case listed there was evidence that an incubation period of not less than five days elapsed between initial administration of the drug and appearance of the reaction and that readministration of a dose not larger than that initially tolerated, under circumstances not suggesting cumulation, led to recurrence of the reaction on at least one occasion. Unfortunately, it is entirely possible that recurrence on readministration was fortuitous in some of the instances listed, and it is highly probable that in some cases that have not been included in the table because the reaction occurred promptly after the "first" dose allergy to the drug really was the cause and the patient had been sensitized by an unreported previous exposure to the drug. In contact dermatitis, patch tests have been considered as readministration, but otherwise skin tests have not been accepted. Cross reactions have not been considered. It will be noted that conjunctivitis does not appear in this table, but certain drugs, such as Larocaine[178] and Antazoline (antistine),[167] have been shown to cause allergic conjunctivitis on topical administration whereas others, such as sulfathiazole[191] and neoarsphenamine,[195] have caused it on systemic administration. Lastly, allergy to proteins and gums has not been considered.

The demonstration that in certain cases a disease is due to allergy to drugs obviously does not prove that this is always the cause of the disease.

(*To be concluded*)

References

1. Definitions of words pertaining to allergy, by the Committee on Nomenclature for the Association of Allergy Clinics of Greater New York. *J. Allergy* **12**:202-210, 1941.
2. Grolnick, M. Contact allergy of skin. *Ann. New York Acad. Sc.* **50**:718-739, 1949.
3. Heinbecker, P. Studies in hypersensitiveness: susceptibility of Eskimos to extract from Toxicodendron radicans (L.). *J. Immunol.* **15**:365-367, 1928.
4. Straus, H. W. Artificial sensitization of infants to poison ivy. *J. Allergy* **2**:137-144, 1931.
5. Bloch. Cited by Chase.[16]
6. Zinsser, H., Enders, J. F., and Fothergill, L. D. *Immunity: Principles and applications in medicine and public health.* 801 pp. New York: Macmillan Co., 1939.
7. Harten, M., and Walzer, M. Allergy to insulin, liver, pituitary, pancreas, estrogens, enzymes and similar substances. *J. Allergy* **12**: 72-105, 1940.
8. Landsteiner, K., and Lampl, H. Untersuchung der Spezifität von Serumreaktionen durch Einführung verscheidenartiger Gruppen in Eiweiss. *Zentralbl. f. Physiol.* **30**:329, 1915.
9. Landsteiner, K., and Jacobs, J. Studies on the sensitization of animals with simple chemical compounds. *J. Exper. Med.* **61**: 643-656, 1935.
10. Landsteiner, K., and Jacobs, J. Studies on sensitization of animals with simple chemical compounds. *J. Exper. Med.* **64**:625-639, 1936.
11. Landsteiner, K., and Jacobs, J. Studies on sensitization of animals with simple chemical compounds. Anaphylaxis induced by arsphenamine. *J. Exper. Med.* **64**:717-721, 1936.
12. Landsteiner, K., and Chase, M. W. Studies on sensitization of animals with simple chemical compounds. Anaphylaxis induced by picryl chloride and 2:4-dinitrochlorobenzene. *J. Exper. Med.* **66**:337-351, 1937.
13. Landsteiner, K., and Chase, M. W. Studies on sensitization of animals with simple chemical compounds: skin sensitization induced by injection of conjugates. *J. Exper. Med.* **73**:431-438, 1941.
14. Landsteiner, K. *The Specificity of Serological Reactions.* 310 pp. Cambridge: Harvard University Press, 1945.
15. Chase, M. W. The allergic state. In *Bacterial and Mycotic Infections of Man.* Edited by R. J. Dubos. Philadelphia: J. B. Lippincott Co., 1948. Chap. 6.
16. Cormia, F. E. Cutaneous sensitization to arsphenamine. *Arch. Dermat. & Syph.* **43**:103-110, 1941.
17. Mulinos, M. G., and Schlesinger, E. Contribution to drug allergy. *Proc. Soc. Exper. Biol. & Med.* **35**:305-307, 1936.
18. Wedum, A. G. Immunological specificity of sulfonamide azoproteins. *J. Infect. Dis.* **70**:173-179, 1942.
19. Landsteiner, K., and Chase, M. W. Experiments on transfer of cutaneous sensitivity to simple compounds. *Proc. Soc. Exper. Biol. & Med.* **49**:688-690, 1942.
20. Rostenberg, A., Jr., and Kanof, N. M. Studies on eczematous sensitizations: specificity of sensitization from point of view of chemical configuration. *J. Invest. Derm.* **6**:201-211, 1945.
21. Longcope, W. T. Serum sickness and analogous reactions from certain drugs, particularly sulfonamides. *Medicine* **22**:251-286, 1943.
22. Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* **71**:123-140, 1942.
23. *Idem.* Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa. *Bull. Johns Hopkins Hosp.* **71**:375-379, 1942.
24. Rich, A. R., and Gregory, J. E. Experimental demonstration that periarteritis nodosa is manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.* **72**:65-68, 1943.
25. Rich, A. R. Hypersensitivity in disease. *Harvey Lectures*, 1946–1947. Pp. 105-147.
26. Burkantz, S. C., Dammin, G. J., Wilson, K. S., Johnson, M. C., and Alexander, H. L. Inhibitory effect of nitrogen mustard (Bis-Betachloroethyl amine) on experimental serum hypersensitiveness. *Proc. Soc. Exper. Biol. & Med.* **72**:21-26, 1949.
27. Dammin, G. J., and Burkantz, S. C. Modification of biologic response in experimental hypersensitivity. *J. A. M. A.* **139**:358-362, 1949.
28. Gordon, E. J. Delayed serum sickness reaction to penicillin. *J. A. M. A.* **131**:727-730, 1946.
29. Rich, A. R. Hypersensitivity to iodine as cause of periarteritis nodosa. *Bull. Johns Hopkins Hosp.* **77**:43-48, 1945.
30. Moore, F. D. Toxic manifestations of thiouracil therapy. *J. A. M. A.* **130**:315-319, 1946.
31. McCormick, R. V. Periarteritis occurring during propylthiouracil therapy. *J. A. M. A.* **144**:1453, 1950.
32. Meyler, L., Hadders, H. N., and Van Rijssel, T. G. Generalized arteritis after treatment with methylthiouracil. *Nederl. tijdschr. v. geneesk.* **94**:1849, 1950. (Abstr. in *J. A. M. A.* **144**:1038, 1950.)
33. Hartcroft, W. S. Generalized granulomatous reaction following sulfonamide therapy. *Canad. M. A. J.* **51**:23-25, 1944.
34. Lederer, M., and Rosenblatt, P. Death during sulfathiazole therapy. *J. A. M. A.* **119**:8-18, 1942.
35. Merkel, W. C., and Crawford, R. C. Pathologic lesions produced by sulfathiazole: report of 4 fatal cases. *J. A. M. A.* **119**:770-776, 1942.
36. Hill, L. W. Treatment of infantile eczema. *J. A. M. A.* **111**:2113-2117, 1938.
37. Cooke, R. A., et al. *Allergy in Theory and Practice.* 572 pp. Philadelphia: W. B. Saunders Co., 1947.
38. Sulzberger, M. B. *Dermatologic Allergy.* 540 pp. Springfield, Ill.: Charles C Thomas, 1940.
39. Sievers, J. J., Morley, G. R., and Samter, M. Fixed anaphylactic sensitization. *J. Allergy* **20**:167-171, 1949.
40. Sherman, W. B. Drug allergy. *Am. J. Med.* **3**:586-600, 1947
41. Beerman, H. Drug eruptions: survey of recent literature. *Am. J. M. Sc.* **218**:446-476, 1949.

42. Rostenberg, A., Jr. Studies on eczematous sensitization. *J. Invest. Dermat.* **8**:345-355, 1946.
43. Chase, M. W. Personal communication.
44. Sulzberger, M. B., and Rostenberg, A., Jr. Acquired specific sensitivity (allergy) to simple chemicals. Method of experimental sensitization and demonstration of increased susceptibility in individuals with eczematous dermatitis of contact type. *J. Immunol.* **36**:17-27, 1939.
45. Underwood, G. B., and Gaul, L. E. Overtreatment dermatitis in dermatitis venenata due to plants. *J. A. M. A.* **138**:570-582, 1948.
46. Sulzberger, M. B., Kanof, A., Beer, R. L., and Lowenberg, C. Sensitization by topical application of sulfonamides. *J. Allergy* **18**: 92-103, 1947.
47. Gottschalk, H. R., and Weiss, R. S. Studies on sensitivity to sulfonamide ointments. *Arch. Dermat. & Syph.* **56**:775-779, 1947.
48. Cole, H. N. Local use of sulfonamide compounds in dermatology. (Report of the Council on Pharmacy and Chemistry.) *J. A. M. A.* **123**:411-417, 1943.
49. Dangers from external use of sulfonamides. (Report of the Council on Pharmacy and Chemistry.) *J. A. M. A.* **128**:1024, 1945.
50. Hopkins, J. G., and Lawrence, H. Sensitization to penicillin. *J. Allergy* **18**:251-262, 1947.
51. Hopkins, J. G., and Lawrence, H. Penicillin therapy in pyogenic dermatoses. *Am. J. M. Sc.* **212**:674-681, 1946.
52. Rostenberg, A., Jr. Eczematous sensitization. *Arch. Dermat. & Syph.* **56**:222-232, 1947.
53. Cook, D. S., and Campbell, D. H. Toxic effects of arsenical compounds as administered in United States Navy in 1934 with special reference to arsenical dermatitis. *U. S. Nav. M. Bull.* **33**: 538-565, 1934.
54. Shoch, A. G., Alexander, L. J., and Long, W. E. Mapharsen in treatment of forty patients following arsphenamine dermatitis. *Arch. Dermat. & Syph.* **42**:919-932, 1940.
55. Taylor, D. R., and Potashnick, R. Quinidine-induced exfoliative dermatitis. *J. A. M. A.* **145**:641, 1951.
56. Weiss, C. R., and Ruedemann, R. Exfoliative dermatitis from potassium sulphocyanate therapy. *J. A. M. A.* **93**:988, 1929.
57. Seymour, W. B., Jr. Poisoning from cutaneous application of iodine. *Arch. Int. Med.* **59**:952-966, 1937.
58. Guy, W. H., Goldmann, B. A., Gannon, G. P., and Slone, J. Acetylglycarsenobenzene in treatment of syphilis. *Arch. Dermat. & Syph.* **42**:1046-1058, 1940.
59. Poole, A. K., and Wehger, R. T. Fatalities in exfoliative dermatitis. *J. A. M. A.* **102**:745-751, 1934.
60. Epstein, E. Cutaneous toxicity of mapharsen. *Am. J. Syph., Gonor. & Ven. Dis.* **25**:225-232, 1941.
61. Meyer, J. H. Exfoliative dermatitis due to codeine. *New Eng. J. Med.* **238**:469, 1948.
62. Kasselberg, L. A. Exfoliative dermatitis due to diethylstilbestrol. *J. A. M. A.* **120**:117, 1942.
63. Hitch, J. M., and Schwartz, W. F. Late toxic results including dermatitis exfoliativa from "slim" (dinitrophenol). *J. A. M. A.* **106**: 2130-2132, 1936.
64. Mandelbaum, H., and Kane L. J. Dilantin sodium posioning: report of case with dermatitis exfoliativa, pyrexia, and hepatic and splenic enlargement. *Arch. Neurol. & Psychiat.* **45**:769-771, 1941.
65. Sundelen, F. Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen. *Acta. med. Scandinav.* Supp. **117**:1-292, 1941.
66. Gruhzit, O. M., Dixon, R. S., et al. Mapharsen in mass treatment of syphilis in clinic for venereal diseases. *Arch. Dermat. & Syph.* **34**:432-454, 1936.
67. Ruskin, D. B. Fulminating dermatitis bullosa medicamentosa due to "mesantoin." *J. A. M. A.* **137**:1031-1035, 1948.
68. Goebel, F. Für und wider die Nirvanolbehandlung der Chorea minor. *Deutsche med. Wchnschr.* **57**:1313-1315, 1931.
69. Farrington, J., and Tamura, J. Cutaneous testing in case of exfoliative dermatitis caused by penicillin. *Arch. Dermat. & Syph.* **56**:807-811, 1947.
70. Winer, N. J., and Baer, R. L. Exfoliative dermatitis due to phenobarbital. *Arch. Dermat. & Syph.* **43**:473-484, 1941.
71. Kierland, R. R. Drug eruptions due to atabrine and resembling lichen planus. *Proc. Staff Meet., Mayo Clin.* **21**:404-408, 1946.
72. Hargrove, U. S. Exfoliative dermatitis from sobisminol mass by mouth. *New Orleans M. & S. J.* **93**:519, 1941.
73. Cohen, A. C., and Glinsky, G. C. Hypersensitivity to streptomycin. *J. Allergy* **22**:63-70, 1951.
74. Johnson, R. D. Generalized exfoliative dermatitis due to sulfadiazine. *J. A. M. A.* **124**:979, 1944.
75. Kasselberg, L. A. Severe pemphigus-like reaction following administration of sulfamerazine. *J. A. M. A.* **123**:1035, 1943.
76. Sutliff, W. D., Helpern, M., Griffin, G., and Brown, H. Sulfonamide toxicity as cause of death in New York City in 1941. *J. A. M. A.* **121**:307-313, 1943.
77. Blank, P. In discussion of Thomas, J. W., and Fenton, M. M. Fatalities and constitutional reactions following use of pontocaine. *J. Allergy* **14**:145-159, 1943.
78. Leard, S. E., Greer, W. E. R., and Kaufman, I. C., Hepatitis, exfoliative dermatitis and abnormal bone marrow occurring during tridione therapy. *New Eng. J. Med.* **240**:962-966, 1949.
79. Plum, P. *Clinical and Experimental Investigations in Agranulocytosis.* London: H. K. Lewis & Co., Ltd., 1937. Case No. 77.
80. Dameshek, W., and Colmes, A. Effect of drugs in production of agranulocytosis with particular reference to amidopyrine hypersensitivity. *J. Clin. Investigation* **15**:85-97, 1936.
81. Falconer, E. H., Epstein, N. N., and Wever, G. K. Purpura haemorrhagica following administration of neoarsphenamine compared with reaction to mapharsen. *Arch. Int. Med.* **58**:495-511, 1936.
82. Falconer, E. H., Epstein, N. N., and Mills, E. S. Purpura haemorrhagica due to arsphenamines: sensitivity in patients as influenced by vitamin C therapy. *Arch. Int. Med.* **66**:319-338, 1940.
83. Falconer, E. H., and Epstein, N. N. Purpura haemorrhagica following neoarsphenamine and bismarsen therapy. *Arch. Int. Med.* **65**:1158-1177, 1940.
84. Maritschak, M., and Markowicz, H. Über einen Fall von Chininiiberempfindlichkeit mit Purpura, vorwiegend der oberen Luft- und Speisewege. *Monatschr. f. Ohrenh.* **67**:410-414, 1933.
85. Norcross, J. W. Quinidine as cause of thrombocytopenic purpura. *New Eng. J. Med.* **242**:53, 1950.
86. McGovern, T., and Wright, I. Purpura hemorrhagica following use of sedormid. *J. A. M. A.* **112**:1687, 1939.
87. Davis, W. C., and Saunders, T. S. Purpura due to iodides. *Arch. Dermat. & Syph.* **53**:644, 1946.
88. Kopeloff, N., and Kopeloff, L. M. Blood platelets in anaphylaxis. *J. Immunol.* **40**:471-481, 1941.
89. Hunter, F. T. Drug or protein allergy as cause of agranulocytosis and certain types of purpura. *New Eng. J. Med.* **213**:663-674, 1935.
90. Loveman, A. B. Toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following arsphenamines. *Ann. Int. Med.* **5**: 1238-1256, 1931.
91. Davidson, E. N., and Shapiro, M. Neutropenia following dinitrophenol with improvement after pentnucleotide and leukocyte cream. *J. A. M. A.* **103**:480-482, 1934.
92. Haunz, E. A., Cardy, J. D., and Graham, C. M. Agranulocytosis due to gantrisin. *J. A. M. A.* **144**:1179-1181, 1950.
93. Wechsler, L. Ein Fall von Agranulozytose durch Lopion. *Wien. klin. Wchnschr.* **50**:1360-1362, 1937.
94. Drake, T. G. Agranulocytosis during therapy with antihistaminic agent methaphenilene (diatrin). *J. A. M. A.* **142**:477, 1950.
95. Volterrani, O. Angina agranulocitica da metiltiouracile. Guarigione. *Minerva Med.* **1**:268-270, 1947.
96. Epstein, N. N., and Falconer, E. H. Effects of neoarsphenamine and mapharsen on formed elements of blood. *Arch. Dermat. & Syph.* **42**:909-918, 1940.
97. Feer, E. Zur lymphatischen Reaktion beim Kinde. Ein Fall von Aleukie nach Nirvanol. *Monatschr. f. Kinderh.* **42**:157-169, 1929.
98. Fisher, S., Holley, H. L., and Fein, G. Agranulocytosis: report of twelve cases in which it followed intensive arsenotherapy for syphilis. *Arch. Dermat. & Syph.* **55**:57-66, 1947.
99. Ehrlich, M. E., and Sussman, L. N. Agranulocytosis following use of pyrithyldione. *J. A. M. A.* **141**:132, 1949.
100. Beebe, R. T., Propp, S., McClintock, J. C., and Versaci, A. Fatal agranulocytosis during treatment of toxic goiter with propylthiouracil. *Ann. Int. Med.* **34**:1035-1040, 1951.
101. Clément, R., and Godlewski, S. Agranulocytose aigüe curable apparue au cours de traitement d'un asthme par un antihistaminique de synthèse. *Bull. et mém. Soc. méd. d. hôp. de Paris* **61**:103-105, 1945.
102. Gorke, H. Auftreten von aplastischer Anämie nach Salvarsan. *München. med. Wchnschr.* **67**:1226-1228, 1920.
103. Curry, J. J. Acute agranulocytosis following sulfadiazine. *J. A. M. A.* **119**:1502, 1942.
104. Filler, W. Puerperal sepsis due to staphylococcus aureus treated successfully with sulfamethylthiazole. *Am. J. Obst. & Gynec.* **41**: 145-150, 1941.
105. Rinkoff, S. S., and Spring, M. Toxic depression of myeloid elements following therapy with sulfonamides: report of 8 cases. *Ann. Int. Med.* **15**:89-107, 1941.
106. Morris, G. N. Agranulocytosis following the use of "M. & B. 693" with report of case associated with abdominal symptoms. *M. J. Australia* **1**:515-518, 1941.
107. Dodd, K., and Wilkinson, S. J. Severe granulocytic aplasia of bone-marrow. *J. A. M. A.* **90**:663-665, 1928.
108. Kennedy, P. C., and Finland, M. Fatal agranulocytosis from sulfathiazole. *J. A. M. A.* **116**:295, 1941.
109. Moore, F. D. Toxic manifestations of thiouracil therapy. *J. A. M. A.* **130**:315-319, 1946.
110. Michelstein, S., and Weiser, N. J. Fatal agranulocytosis due to trimethadione (tridione). *Arch. Neurol. & Psychiat.* **62**:358-360, 1949.
111. Blanton, W. B., and Owens, M. E. B., Jr. Granulocytopenia due probably to "pyribenzamine." *J. A. M. A.* **134**:454, 1947.
112. Pelner, L. Iodine allergy. *J. Lab. & Clin. Med.* **27**:1150-1154, 1942.
113. Meyer, A. H. Thrombocytopenic purpura: case caused by sulfadiazine. *Calif. & West. Med.* **60**:98, 1944.
114. Goldbloom, A. A., Greenwald, L., and Reinstein, H. Toxic reactions to sulfapyridine: acute hemolytic anemia, leucemoid reaction, and purpura in three separate cases. *J. Lab. & Clin. Med.* **27**:139-147, 1941.
115. McCarthy, F. P., and Wilson, R., Jr. Blood dyscrasias following arsphenamines. *J. A. M. A.* **99**:1557-1563, 1932.
116. Hurd, R. W., and Jacox, R. F. Thrombopenic purpura developing as complication of sulfathiazole and sulfadiazine therapy. *J. A. M. A.* **122**:296-298, 1943.
117. Newcomb, P. B., and Deane, E. W. Thiourea causing granulopenia and thrombopenia. *Lancet* **1**:179, 1944.
118. Ellman, P., and Lawrence, J. S. Agranulocytosis with purpura hemorrhagica following gold therapy. *Brit. M. J.* **2**:622, 1935.

119. Mitchell, H. S., and Denton, R. L. Overdosage with dexedrine. *Canad. M. A. J.* **62**:594, 1950.

120. Bloom, N., Lynch, J. P., and Brick, H. "Mesantoin" poisoning with aplastic anemia and recovery. *J. A. M. A.* **138**:498, 1948.

121. Rein, C. R., and Wise, F. Mapharsen in treatment of syphilis in office practice. *J. A. M. A.* **113**:1946-1952, 1939.

122. Stephens, D. J. Aplastic anemia during treatment of syphilis with arsphenamines. *Am. J. Syph.* **15**:333-349, 1931.

123. Meyer, L., and Perlmutter, M. Aplastic anemia due to sulfathiazole. *J. A. M. A.* **119**:558, 1942.

124. Mackay, R. P., and Gottstein, W. K. Aplastic anemia and agranulocytosis following tridione. *J. A. M. A.* **132**:13-16, 1946.

125. Watson, C. J., and Spink, W. W. Effect of sulfanilamide and sulfapyridine on hemoglobin metabolism and hepatic function. *Arch. Int. Med.* **65**:825-846, 1940.

126. Townsend, T., and Mulcahy, T. Sulfanilamide in treatment of urological infections. *New York State J. Med.* **38**:833-835, 1938.

127. Lyons, R. H., and Balberor, H. Febrile reactions accompanying readministration of sulfathiazole. *J. A. M. A.* **118**:955-958, 1942.

128. Talbot, T. R., Jr., and Adcock, J. D. Febrile reactions resulting from readministration of sulfadiazine. *Am. J. M. Sc.* **205**:841-846, 1943.

129. Kent, G. T., and Diefendorf, W. Clinical study of sensitivity to sulfathiazole. *Am. J. M. Sc.* **209**:640-645, 1945.

130. Dowling, H. F., Hirsh, H. L., and Lepper, M. H. Toxic reactions accompanying second courses of sulfonamides in patients developing toxic reactions during previous course. *Ann. Int. Med.* **24**:629-633, 1946.

131. Dowling, H. F., and Lepper, M. H. "Drug fever" accompanying second courses of sulfathiazole, sulfadiazine and sulfapyridine. *Am. J. M. Sc.* **207**:349-353, 1944.

132. Fink, H. W., and Wilson, J. L. Evaluation of dangers of repeated administration of sulfadiazine and sulfathiazole in children. *J. Pediat.* **22**:513-517, 1943.

133. Dowling, H. F., and Lepper, M. H. Toxic reactions following therapy with sulfapyridine, sulfathiazole and sulfadiazine. *J. A. M. A.* **121**:1190-1194, 1943.

134. Ottenberg, R., and Spiegel, R. Present status of non-obstructive jaundice due to infectious and chemical agents. *Medicine* **22**:27-71, 1943.

135. Sugg, F. S. Acquired sensitivity to cinchophen. *Am. J. M. Sc.* **195**:473-479, 1938.

136. Fitzgibbon, P., and Silver, B. Toxic necrosis of liver following use of sulfanilamid. *Calif. & West. Med.* **50**:123-125, 1939.

137. Peterson, O. L., Deutsch, E., and Finland, M. Therapy with sulfonamide compounds for patients with damage to liver. *Arch. Int. Med.* **72**:594-612, 1943.

138. Shookhoff, C., and Lieberman, D. L. Hypersensitiveness to acetylsalicylic acid expressed by angina pectoris syndrome with and without urticaria. *J. Allergy* **4**:506-512, 1933.

139. Moore, J. E., and Keidel, A. Dermatitis and allied reactions following arsenical treatment of syphilis. *Arch. Int. Med.* **27**:716, 1921.

140. Peck, S. M., and Feldman, F. F. Sensitivity reactions to aureomycin. *J. A. M. A.* **142**:1137-1139, 1950.

141. Frumess, G. M. Allergic reaction to dinitrophenol. *J. A. M. A.* **102**:1219, 1934.

142. Gottlieb, P. Sensitivity to mercurial diuretics. *Ann. Allergy* **6**:518-533, 1948.

143. Corson, E. F., and Sidlick, D. M. Urticaria from phenolphthalein. *J. A. M. A.* **78**:882, 1922.

144. Sanchez-Cuenca, B. Penicillinosis and hypersensitiveness to penicillin. *J. Allergy* **21**:176-178, 1950.

145. Hobson, L. B., Tompsett, R., Muschenheim, C., and McDermott, W. Laboratory and clinical investigation of dihydrostreptomycin. *Am. Rev. Tuberc.* **58**:501-524, 1948.

146. Riese, J. A. Toxic reactions to aureomycin. *J. M. Soc. New Jersey* **46**:467, 1949. (Cited by Parets, A. D. Angioneurotic edema and rash due to aureomycin. *J. A. M. A.* **143**:653, 1950.)

147. Kolodny, M. H., and Denhoff, E. Reactions in penicillin therapy. *J. A. M. A.* **130**:1058-1061, 1946.

148. Madden, J. F. Reaction due to sulfapyridine in treatment of dermatitis herpetiformis. *Arch. Dermat. & Syph.* **47**:695, 1943.

149. Rowe, A. H. *Clinical Allergy due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes.* 812 pp. Philadelphia: Lea and Febiger, 1937. Chap. VI.

150. Gelfand, M. L. Hypersensitivity to mercuhydrin with positive skin test to post-treated mercuhydrin serum. *J. Allergy* **20**:404-410, 1949.

151. Schiff, L. F., and Schiff, L. J. Anaphylactic reaction to intravenous administration of procaine. *Anesthesiology* **10**:753, 1949.

152. Randolph, T. G., and Rawling, F. F. A. Bronchial asthma as manifestation of sulfonamide sensitivity. *J. A. M. A.* **126**:166, 1944.

153. Greenberg, L. A. *Antipyrine: A critical bibliographic review.* 135 pp. New Haven: Hillhouse, 1950.

154. Barton, R. L., and O'Leary, P. A. Fixed drug eruption produced by diphenylhydantoin sodium. *Arch. Dermat. & Syph.* **48**:413, 1943.

155. Short, C. L., and Bauer, W. Cinchophen hypersensitiveness: report of 4 cases and review. *Ann. Int. Med.* **6**:1449-1464, 1933.

156. Lesigang, W. Die Nirvanolkrankheit. *Monatschr. f. Kinderk.* **40**:289-302, 1928.

157. Occupational dermatitis due to penicillin. *J. A. M. A.* **136**:730, 1948.

158. Poole, A. K. Drug reactions from barbital (veronal) and phenobarbital (lumina). *Yale J. Biol. & Med.* **1**:345-351, 1929.

159. Newman, B. A. Phenolphthalein intoxication. *J. A. M. A.* **101**:761-764, 1933.

160. Bechet, P. E. Etiologic role of iodized table salt in iododerma. *J. Invest. Dermat.* **8**:401-417, 1947.

161. Goodman, M. H., and Arthur, R. D. Fixed eruptions: report of unusual condition due to sulfanilamide. *Arch. Dermat. & Syph.* **43**:692-697, 1941.

162. Thompson, A. R. "M. & B. 693" rashes with particular reference to acute exanthemata. *Brit. M. J.* **2**:13, 1939.

163. Shaffer, B., Lentz, J. W., and McGuire, J. A. Sulfathiazole eruptions. *J. A. M. A.* **123**:17-23, 1943.

164. Gabrilove, J. L., and Kent, M. F. Sensitivity to thiouracil: report of 3 cases. *J. A. M. A.* **124**:504, 1944.

165. Harris, M. C., and Shute, N. Eczematoid dermatitis following ingestion of "Pyribenzamine hydrochloride," N. N. R. tablets. *J. Allergy* **18**:408-412, 1947.

166. Nelson, L. M. Dermatitis medicamentosa due to undecylenic acid. *J. Invest. Dermat.* **14**:75, 1950.

167. Mosko, M. M., and Peterson, W. L. Sensitization to antistine. *J. Invest. Dermat.* **14**:1, 1950.

168. Laden, E. L., and Rubin, L. Experimental sensitization to butesin: experimental study on range of specificity. *J. Invest. Dermat.* **11**:119-125, 1948.

169. Cope, F. P. Contact dermatitis due to cod liver oil. *Arch. Dermat. & Syph.* **46**:140, 1942.

170. Sulzberger, M. B., Baer, R. L., and Kanof, A. Clinical uses of 2, 3-dimercaptopropanol (BAL): skin sensitization to BAL. *J. Clin. Invest.* **25**:488-496, 1946.

171. Cummer, C. L. Dermatitis of eyelids caused by dionin. *Arch. Dermat. & Syph.* **23**:68, 1931.

172. Rein, C. R., and Kanof, N. B. Sensitivity to intracaine. *J. Invest. Dermat.* **11**:311, 1948.

173. Theodore, F. H. Hypersensitivity to larocaine. *Arch. Ophth.* **20**:474-476, 1938.

174. Gaul, L. E., and Underwood, G. B. Dermatitis venenata from organomercurial compounds with comparison of their pharmacological action on normal and injured skin. *J. A. M. A.* **140**:860-865, 1949.

175. Jordan, J. W., and Osborne, E. D. Contact dermatitis from opium derivatives. *J. A. M. A.* **113**:1955-1957, 1939.

176. Frei, W. Über willkürliche Sensibilisierung gegen chemisch definierte Substanzen. *Klin. Wchnschr.* **7**:1026-1031, 1928.

177. Downing, J. G., Hanson, M. C., and Lamb, M. Use of 5-nitro-2-furaldehyde semicarbazone in dermatology. *J. A. M. A.* **133**:299-306, 1947.

178. Perera, C. A. Ocular sensitivity to nupercaine. *Arch. Ophth.* **24**:344-346, 1940.

179. Heller, N. B. Acute dermatitis due to opium preparations. *Arch. Dermat. & Syph.* **24**:417, 1931.

180. Goodman, H. Dermatitis due to preparation and administration of penicillin solution. *Arch. Dermat. & Syph.* **54**:206-208, 1946.

181. Skinner, L. C. Contact dermatitis due to phenolphthalein. *Arch. Dermat. & Syph.* **59**:338, 1949.

182. James, B. M. Procaine dermatitis. *J. A. M. A.* **97**:440-442, 1931.

183. Keil, H., and Trosow, A. Eczematous contact dermatitis due to streptomycin. *Ann. Allergy* **6**:435-438, 1948.

184. Abramowitz, E. W. Hazards of external use of sulfonamide compounds. *Arch. Dermat. & Syph.* **50**:289-299, 1944.

185. Strauss, M. J. Group sensitivity to local anesthetics. *J. Invest. Dermat.* **8**:403-407, 1947.

186. Ellis, F. A., and Bundick, W. R. Reactions to local use of thephorin. *J. Invest. Dermat.* **13**:25-28, 1949.

187. Sherman, W. B., and Cooke, R. A. Dermatitis following use of pyribenzamine and antistine. *J. Allergy* **21**:63-67, 1950.

188. Goldman, L., Feldman, M. D., and Altmeier, W. A. Contact dermatitis from topical tyrothricin and associated with polyvalent hypersensitivity to various antibiotics: report of case. *J. Invest. Dermat.* **11**:243, 1948.

189. Cook, S. S., and Campbell, H. D. Toxic effects of arsenical compounds employed in treatment of disease in United States Navy, 1934. *U. S. Nav. M. Bull.* **34**:97-143, 1936.

190. Stimson, W. H., and McKusick, V. A. Febrile reactions to quinidine. *Am. J. M. Sc.* **221**:440-443, 1951.

191. Bunting, J. J., and Levan, N. E. Toxic reactions of sulfaguanidine therapy. *J. A. M. A.* **128**:773, 1944.

192. Park, R. G. Pathogenesis of sulphonamide neutropenia. *Lancet* **1**:401-403, 1944.

193. Van Winkle, W. W., et al. Clinical toxicity of thiouracil, survey of 5745 cases. *J. A. M. A.* **130**:343-347, 1946.

194. Glicklich, E. A., and Sherman, D. S. Toxic effects of sulfathiazole used in treatment of chancroidal infection. *Arch. Dermat. & Syph.* **43**:992-996, 1941.

195. Fuchs, D. Fixe salvarsanexantheme. *Deutsche med. Wchnschr.* **45**:1276, 1919. (Cited by Moore and Keidel.[139])

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 37491

PRESENTATION OF CASE

First admission. A fifty-two-year-old woman was admitted to the hospital because of vaginal bleeding and lower-back pain.

Four years before admission a diagnosis of adenocarcinoma of the uterine fundus was established by biopsy and intrauterine radium therapy was carried out. Three years before entry curettage had shown residual adenocarcinoma and she was again treated with intrauterine radium. Seven months prior to admission she developed vague lower-back pain and subsequently had irregular vaginal bleeding.

Diabetes mellitus had been discovered four years prior to entry; this was adequately controlled by diet without insulin.

Physical examination was negative except for obesity. The blood pressure was 130 systolic, 80 diastolic. Examination of the blood showed a hemoglobin of 11.9 gm., a white-cell count of 7600 and a fasting blood sugar of 160 mg. per 100 cc.

Panhysterectomy and appendectomy were performed; the pathological diagnosis was adenocarcinoma of the uterus.

Final admission (13 years later, at the age of sixty-five). One year after discharge the diabetes could no longer be controlled by diet alone and insulin therapy was started. At first she was reasonably well regulated on 20 units of protamine zinc insulin daily, but the requirements steadily increased until six years before admission she required 80 units of protamine zinc insulin and 20 units of regular insulin. Even with this dosage her diabetes was not well controlled, and she developed severe pruritus and leukoplakia of the vulva. She was admitted to the hospital, and with strict regulation of the diabetes the lesions cleared quickly and completely. In the hospital she required 32 units of protamine zinc insulin and 16 units of regular insulin. For the next three years she was moderately well controlled on this dosage; her weight remained steady, and she felt well except for an occasional episode of furunculosis and cystitis. Three years before admission the diabetes again became poorly controlled and the insulin was increased to 80 units of protamine zinc and 56 units of regular insulin. She developed a cellulitis of the foot that necessitated hospitalization; on the above insulin dosage and penicillin the diabetes was adequately controlled and the cellulitis readily responded. She was well controlled for the next three years on the above dosage schedule, which was reduced to 64 units of protamine zinc and 56 units of regular insulin shortly before admission.

Two weeks prior to entry the patient developed severe sharp, stabbing right-chest pain. It was most severe under the right breast and radiated along the eighth rib posteriorly to the subscapular area. It was accentuated by body movement, inspiration and cough. One week prior to admission she had chilly sensations and a temperature of 102°F. With oral penicillin, one tablet every four hours, the fever subsided, but the pain persisted; it was of such severity that she was bedridden and unable to sleep despite codeine medication. For four days before admission she had marked polydipsia, polyuria and orange sugar reactions on the urine.

Physical examination revealed a flushed, obese woman in acute distress, complaining of right chest pain. The chest was symmetrical. The right chest was markedly tender to superficial palpation. This was most marked under the right breast and along the eighth rib from the midclavicular line to the subscapular area. No skin lesions or masses were noted. The neck veins were flat. Fine to medium moist rales were present at both lung bases. The heart and abdomen were negative. A 2-cm. circumscribed dry ulcer was present on the plantar surface of the right great toe. Dorsalis-pedis pulses were present. There was + ankle edema. Vibration sense was reduced in both lower extremities, but otherwise the neurologic examination was normal. Pelvic examination showed a stenosed introitus admitting only the tip of the small finger. Rectal examination was negative.

The temperature was 101°F., the pulse 100 and the respirations 20. The blood pressure was 130 systolic, 76 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ albumin reaction, a + acetone reaction and an orange sugar reaction; the sediment contained an occasional white cell and red cell. Cultures of the urine grew *B. coli* and beta-hemolytic streptococci. Examination of the blood revealed a white-cell count of 17,800, with 80 per cent neutrophils, and a hemoglobin of 15 gm. The sedimentation rate was 1.1 mm. per minute (corrected). The fasting blood sugar was 238 mg. and the nonprotein

nitrogen 24 mg. per 100 cc.; the carbon dioxide was 29.7 milliequiv. per liter. A blood Hinton test was negative. Blood cultures were negative. A culture of the sputum yielded abundant *Staphylococcus aureus*. Roentgenograms of the chest showed the diaphragm to be somewhat higher than had been noted on previous films. There was some fluid in the right pleural space and a linear density was present in the left lower lateral lung field. Indefinite linear densities were present in the right lower lobe (Fig. 1). X-ray films of the spine showed only mild degenerative changes. An electrocardiogram was negative to normal. A lumbar puncture showed normal dynamics, 76 mg. of protein per 100 cc. and no cells. Thoracentesis performed in the right posterior axillary line between the eighth and ninth ribs yielded 250 cc. of reddish-yellow fluid with a specific gravity of 1.017 and 13,800 cells per cubic mm., of which 3900 per cu. mm. were white cells. Smears of the fluid stained with Ziehl–Neelsen and Gram stain were negative for bacteria.

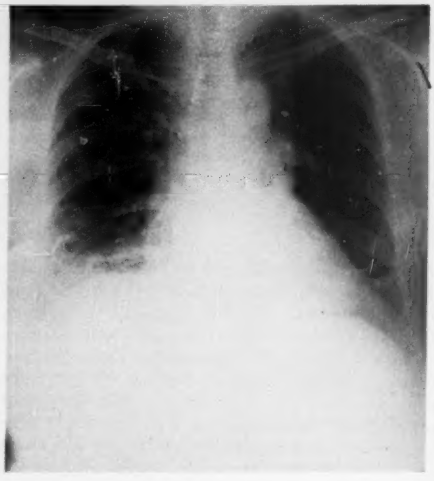


FIGURE 1.

She continued to have severe chest pain, which was relieved only transiently by paravertebral blocks, intercostal blocks, demerol or codeine. The temperature continued between 99 and 100°F., with the pulse rate between 90 and 100 and the respirations between 20 and 25. She was placed on the hospital 1500-calorie diabetic diet and given 65 units of protamine zinc insulin daily and regular zinc insulin as indicated by the two-hour urine tests. There was some difficulty in regulating the diabetes. On the eighth day, after 80 units of protamine zinc and 80 units of regular insulin, the urine gave an olive sugar reaction and contained no acetone; the fasting blood sugar was 276 mg. per 100 cc. A chest film showed a definite increase in the amount of fluid in the right pleural space. A white-cell count was 18,800 per cubic mm. A second thoracentesis above the ninth rib failed to reveal any fluid. On the tenth day she became disoriented and incontinent of urine. Breathing became labored and the pupils were contracted; the reflexes were hypoactive and rales were heard throughout both lungs. She was started on penicillin therapy. On the eleventh day respiratory distress became severe and she died. On the day of death the white-cell count was 40,400. An electrocardiogram showed an idioventricular rhythm of 90 with a QRS interval of 0.16 second and a QT interval of 0.32 second. The Q waves were present in Leads 3 and AVF; the ST segment was depressed in Leads 1, 2 and AVL and elevated in Leads 3, AVR and AVF; the T waves were very high and wide in Leads 1 and AVL and inverted in Leads 2, 3, AVR and AVF.

Differential Diagnosis

DR. CHARLES L. SHORT*: I should like to start by seeing the x-ray films so that we may have all the information available about the last admission.

DR. STANLEY M. WYMAN: The first film was taken three years before admission and the subsequent films were all taken during the final admission. The original film shows no localized disease in the lungs and the heart shadow is not remarkable except for a very small degree of prominence of the left ventricle. The later film shows the elevation of the diaphragm described in the protocol. There are now linear densities in both lung fields; the following day they are more sharply defined. There is probably a small quantity of fluid in the right chest on that second day's examination, which is quite well seen in the lateral view lying posteriorly. The films of the thoracic spine do not show any localized lesion. The painful right eighth rib does not seem to display any definite destruction or fracture. The last two films of the chest, taken with the patient lying on her back, show an increased amount of fluid in the right pleural space. They show increasing prominence of the hilar and pulmonary shadows consistent with some degree of pulmonary congestion.

DR. SHORT: Can you tell whether the shape and size of the heart have changed?

DR. WYMAN: It does not seem to have changed appreciably from the original film.

DR. SHORT: There is elevation of the right diaphragm, I am sure, compared to the early film. Are the linear densities consistent with infarction?

DR. WYMAN: I would think of infarction first.

DR. SHORT: Would you say they were old or recent?

*Associate physician, Massachusetts General Hospital.

DR. WYMAN: They have changed somewhat in the course of a single day, which makes me think they were quite fresh. They are quite linear, so that they have been there long enough to show some resolution.

DR. SHORT: The elevation of the diaphragm is consistent with that diagnosis?

DR. WYMAN: Yes — as is the presence of fluid. Atelectasis cannot be distinguished from infarcts, of course.

DR. BENJAMIN CASTLEMAN: Would a linear density appear in that period of time? I would not think that an infarct would become linear in less than about a month.

DR. WYMAN: I think what we see may be the associated atelectasis; that can be seen very early.

DR. SHORT: A matter of a few days?

DR. WYMAN: Yes. To see the actual infarction, one would have to rotate the patient very carefully to get the lesion in profile. Maybe we are seeing the atelectasis.

DR. SHORT: I shall first try to decide whether or not the adenocarcinoma of the uterine fundus was concerned in the cause or causes of this patient's death. The tumor was evidently slow-growing and not highly malignant, since it was removed surgically four years after the first radium treatment. Late blood-borne metastases from such a tumor do occasionally travel to bone and to the lungs, but the seventeen-year time interval seems almost too long. I do not know the literature well enough to say whether or not there may be some rare exceptions. The patient's initial chest pain two weeks before the last admission could, of course, have been caused by a metastasis to the ribs, to the pleura or even to the spine. But the fever and rapidly downhill course seem difficult to interpret on the basis of metastatic carcinoma of the uterus. Furthermore, at the last admission there was no evidence of a local recurrence of the tumor in the pelvis as far as could be determined by physical examination. I think that I shall have to decide, then, that the carcinoma was probably cured by the combination of radiation and surgery and should be classified as past history.

What are some other possible explanations of this severe unremitting chest pain? It was apparently along the course of the eighth rib on the right. It was accentuated by respiration, by cough and by movement of the body and was accompanied by severe tenderness to the superficial palpation. The pain and the tenderness could be referred from either a spinal or an intraspinal lesion, but I am not helped in that regard either by the x-ray findings in the spine or by the spinal-fluid findings. The latter shows an increase in total protein, which might be accounted for by a subclinical diabetic neuropathy. We have seen diabetics with radicular pain somewhat of this nature, the origin of which was obscure and could not be accounted for in any other way and was assumed to be a diabetic neuropathy. I suppose that I might think of explaining this patient's pain on this basis, but I would prefer to think that it was intimately connected with the cause of death.

If I assume that this pain originated in a rib, what are the most common causes of severe pain in bone? I should say malignancy, usually metastatic, and infection. To take up malignancy first, I have to think of some other independent primary malignancy, especially since a study by Smith* has shown that patients with carcinoma of the body of the uterus have a tendency to develop primary cancer elsewhere. In his series the incidence was as high as 5 per cent. The patient may have had a primary tumor elsewhere with metastases to the chest, but there is no clue to its existence either in the history or in any of the data presented in the protocol. Therefore I shall merely mention that possibility in passing.

Before going on to consider infection, I should like to speak of two other diagnostic possibilities. The first, which again I shall merely mention, is a coronary occlusion. The chest pain is far from typical, and the negative electrocardiogram on admission is certainly against this diagnosis. However the final electrocardiogram suggests posterior infarction — but not a recent one. Although coronary disease, often with infarction, is commonly found at autopsy in diabetics of long standing who have reached this age, I do not see any reason to consider this diagnosis in explaining this patient's death.

The second possibility is pulmonary infarction. The x-ray studies are consistent with this diagnosis, including the pleural effusion, and it is possible that these infarcts were of recent vintage. Certainly agonizing pain is common in pulmonary infarction; tenderness of the chest wall is also a characteristic finding. But unless she had subsequent infarctions, it hardly seems likely that the pain would have lasted a total of three weeks in spite of various therapeutic measures, including nerve block. That is the reason that I doubt that the pain, at least, was caused by pulmonary infarction. The downhill course in the last two days and death might be explained by a larger pulmonary embolus. In spite of the suggestive x-ray evidence, I do not believe that pulmonary infarctions are connected with the cause of her death.

This patient was a severe diabetic of seventeen years' standing. She had infections in the past that had readily responded to treatment, but she did represent a patient who was likely to develop a severe, widespread infection, especially if it was not recognized early and adequately treated. This brings me back to the second cause of intractable pain in bone, which is infection.

*Smith, G. V. Carcinoma of endometrium: review with results of treatment through 1935. *New Eng. J. Med.* **225**:608-615, 1941.

I think that she may have had infection of the right chest wall including the rib, with pleural effusion secondary to that, but without actual bacterial invasion of the pleural cavity — at least at the time of the tap. The tap, as you remember, showed a rather low white-cell count and no bacteria on smear. The primary source of this infection remains obscure — perhaps from the urinary tract or even from the ulcer on the great toe, which was described in the protocol as dry. It seems very likely to me that this time the abundant growth of *Staphylococcus aureus* from the sputum was not due to harmless inhabitants of the nasopharynx but represented a real infection of the lung with these organisms. I think we might bring in the x-ray picture in the lungs and regard the apparent infarctions as septic rather than as the ordinary type and as part of a generalized staphylococcus septicemia. The uninfected pleural fluid could have arisen from a septic focus in the right lung or even from an abscess below the right diaphragm, but again the persistence of the pain makes me think that it more likely originated in the chest wall. The patient's rather sudden downhill course brings up the possibility of other metastatic foci; one or more may have been operative in the brain or even in the myocardium, with death from rupture into the pericardium. Such was the sequence of events in a patient, also a diabetic, who was presented at one of these exercises several years ago.

Before concluding, I should like to bring up one of the most interesting points in this case history, the electrocardiogram taken on the day of death. This tracing showed an idioventricular rhythm, high T waves in two leads, widened QRS complexes and alterations of the ST segment. These findings seem highly suggestive of potassium intoxication. However, after comparing it with tracings from patients who were known to have this form of intoxication and after conferring with one of my electrocardiographer colleagues, I reached the decision that the tracing was not characteristic enough to make a diagnosis of this form of intoxication without additional evidence, clinically or from the laboratory. Potassium intoxication ordinarily occurs in severe renal disease with anuria or oliguria. There was no evidence of such in this patient, — certainly none on admission, — although she might have rapidly developed uremia in a week or so from a severe renal infection, such as necrotizing papillitis, which is found in diabetics. The next most likely cause of potassium intoxication would be adrenocortical insufficiency, but there is nothing to suggest this condition in the other findings. Potassium intoxication with hyperkalemia can occur occasionally from a combination of factors such as were operative in this case — tissue destruction, fever and acidosis, but it would seem doubtful that it could originate from these causes in a patient who apparently had polyuria and presumably was actually excreting an increased amount of potassium. The clinical picture of potassium poisoning with flaccid paralysis and loss of reflexes was not present, but it may not appear in patients with potassium intoxication who die rapidly in uremia. The electrocardiographic findings are, I believe, not explainable on the basis of potassium intoxication. I think they may represent those found in a very toxic dying patient who probably had at least some coronary-artery disease or, as I suggested, actual bacterial invasion of the myocardium.

In conclusion, I should like to propose the diagnosis of staphylococcus septicemia with foci in the chest wall and lungs and possibly in the myocardium and brain.

DR. ALFRED KRANES: Am I correct about the failure to find fluid at the chest tap after the chest film was taken that showed an increase in fluid?

DR. CASTLEMAN: Yes; fluid was obtained only at the first tap.

DR. KRANES: I wonder whether the fact that the temperature responded very readily to oral penicillin indicated that she may possibly have had pneumonia to start with and that the changes in the x-ray film were due to residual empyema. Can you find much objection to that, Dr. Short?

DR. SHORT: That is certainly possible. I thought the response to penicillin, even in that small dose, was somewhat in favor of an infectious process going on at the time it was given. How would you explain the subsequent events and other findings?

DR. KRANES: I do not know; diabetics reveal so many conditions at post-mortem examination. I was only concerned with the chest and the fever. I am a little surprised that no pus or fluid was obtained on the tap at the time the films showed quite a good deal of fluid. It may have been loculated.

DR. SHORT: I did not attempt to speculate concerning why they did not obtain the fluid that was shown there by x-ray examination. The fluid had a rather low cell count on which to presume that she had actual empyema.

DR. KRANES: The fluid that was obtained certainly was not pus, but sometimes clear fluid may be withdrawn in the periphery of purulent fluid.

DR. CASTLEMAN: The fluid was cultured and showed no growth.

Dr. Harwood, you saw this patient; will you tell us the opinion on the ward?

DR. REED HARWOOD: The Service was lead astray in this case through paying undue attention to the diabetic neuropathy. I think the diagnosis of neuropathy was justified on the basis of the loss of ankle jerks, diminished vibration sense, possibly the diminished knee jerks and the high spinal-fluid protein. However, it should be pointed out that these findings are extremely common in elderly diabetics; such patients often have little in the way of symptoms. On the other hand, the degree of pain that this patient had was very unusual for a

diabetic neuropathy. I myself thought that she may have had an abscess under the diaphragm or possibly a metastatic nodule near the right eighth nerve root.

I want to add that there seems to be a tendency to blame any pain that a diabetic has on a neuropathy. That has occurred a number of times in recent months when the pain was clearly typical of some other disorder, as, for example, a ruptured intervertebral disk. Great caution should be exercised in making a diagnosis of diabetic neuropathy.

DR. SHORT: I tried to make the point in my discussion that one probably should not explain pain of this nature by diabetic neuropathy without exhaustive study. Do you think it is reasonable, even after other causes have been excluded? I have seen two patients in whom we finally fell back on a diagnosis of diabetic neuropathy after long observation and adequate study. Is it possible to have such severe pain?

DR. HARWOOD: It has apparently been reported, but I have not seen such a case. In this case I was certain it was not neuropathy, because the patient suffered excruciating pain on the least motion, such as turning over in bed. Sitting up was impossible, getting onto a bed pan was a very painful operation, and coughing, breathing and even talking were painful.

CLINICAL DIAGNOSES

Bronchopneumonia.
Diabetes mellitus.

DR. SHORT'S DIAGNOSIS

Staphylococcal septicemia, with foci in the chest wall and lungs and possibly in the myocardium and brain.

ANATOMICAL DIAGNOSES

Empyema, loculated, right, communicating with chest, wall abscesses, multiple.
(*Diabetes mellitus.*)
Pneumonia, focal, with organization, right lower lobe.
Pulmonary atelectasis, extensive, right lower lobe.
Hydrothorax, right.
Intercapillary glomerulosclerosis, slight.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: When the skin over the right chest was separated, we found numerous abscesses in the subcutaneous tissue of the right chest wall that varied in size from millimeters to centimeters; the largest abscess was located over the eighth rib anteriorly and communicated directly with the pleural cavity to form an extensive empyema over the right lower lobe. There were numerous tracts between the abscesses. In addition there was a hydrothorax; that is, the empyema was separate from the clear fluid in the rest of the chest, which amounted to about a liter and a half. That is probably what was tapped, rather than the empyema.

DR. SHORT: Or the empyema might have formed after the first tap.

DR. CASTLEMAN: Probably not, because it looked old — perhaps a week old.

There were no abscesses in the chest wall or in the pleural cavity on the left side at all. The lung beneath the abscess was quite atelectatic; on section, near the surface, it was slightly infected. I suppose that the original infection was a pneumonia that led to the empyema and that, in turn, spread into the subcutaneous tissue of the chest wall. The culture of the empyema at autopsy showed colon bacilli and nonhemolytic streptococci. It is quite possible that there had been a *Staphylococcus aureus* but it was no longer present because of the antibiotic treatment. We also found a few yeast cells, which we are now finding quite often after the antibiotics do their job.

There was nothing wrong with the heart, and the areas in the lung were just foci of atelectasis — no evidence of infarction. Perhaps because of the pain, the patient held the chest rigid enough to produce plate-like atelectasis on both sides. There was a mild degree of intercapillary glomerulosclerosis but no pyelonephritis. The liver showed a mild degree of cirrhosis, postatrophic type, but I am sure it was working all right.

DR. SHORT: Was the brain examined?

DR. CASTLEMAN: Yes; it was negative. There were no abscesses anywhere else.

DR. SHORT: Can you explain the sudden death? Or the electrocardiographic findings?

DR. CASTLEMAN: No. We made several sections of the heart; they showed nothing abnormal and the coronary arteries were patent. Certainly there was enough sepsis for it to have been the major factor.

CASE 37492

PRESENTATION OF CASE

A nineteen-year-old girl was admitted to the hospital because of failure to menstruate.

The patient had never had any vaginal bleeding. There had been no definite molimina; there were occasional episodes of lower-abdominal pressure that were attributed to gastrointestinal stasis. Five years before entry her voice became deep, and there was progressive deepening during the subsequent years. For the four years before admission there was a noticeable growth of hair on the face, arms, legs and thighs and, during the year before admission, on the chest. For two years the clitoris had been approximately one inch long. There had been no increase in height during the two to three years before entry, but she had grown rapidly from the age of eleven to the age of sixteen

years to attain a height of five feet, eight and three-fourths inches (her mother was five feet, seven inches and her father five feet, ten and a half inches tall). She had noted that her reactions to people and problems were more masculine than those of her girl friends. She had not recognized any definite sex urge.

The patient had had measles, mumps and chickenpox in early childhood. She had no siblings. Her mother had begun to menstruate at the age of sixteen.

Physical examination revealed an intelligent, cooperative girl with large bones and rather well developed musculature. There was excess hair on the face, arms, legs and thighs and in the perianal region, with a smaller amount of light hair over the breasts and abdomen. The pubic hair was female in distribution. The skin was somewhat dry and there was a mild acneform eruption on the face. The larynx was prominent. The breasts were small but appeared to contain a little glandular tissue. The heart, lungs and abdomen were not remarkable. The labia were well defined. The clitoris was enlarged, being 2 cm. in length. The vagina admitted one finger. The cervix was small and soft; the fundus could not be made out. On rectal examination a 5-by-5-cm. firm mass was felt to the right and behind the cervix.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 11.7 gm. and a white-cell count of 9200 with a normal differential. A urine specific gravity of 1.030 was normal. The basal metabolic rate was −13. Quantitative determination of FSH (follicle-stimulating hormone) was positive for 10 and 30 mouse units per 100 cc. of urine and negative for 50 mouse units per 100 cc. of urine. (In the method used this level was that found in postmenopausal women.) A 17-ketosteroid assay showed 8.0 mg. per twenty-four hours and 9.0 mg. per twenty-four hours on two determinations.

On the eighth day an operation was performed.

Differential Diagnosis

Dr. Janet W. McArthur*: My task is to determine the nature of a process whose principal manifestations, were primary amenorrhea, frank virilization and the presence of a pelvic tumor. The points that are especially striking on physical examination are the well developed musculature, the excessive hair on the face and limbs, acne, the small breasts and cervix, the large clitoris and the 5-by-5-cm. mass in the right vault. From this combination of findings it is clear that I am not dealing with a case of simple hirsutism but rather with one exhibiting all the stigmas of virilism. The points in the laboratory examination that seem most important are the normal level of 17-ketosteroid excretion and the postmenopausal level of follicle-stimulating hormone (FSH).

The lesions that must be considered in the differential diagnosis are so diverse in character that it will be convenient to group them under three headings — lesions of the adrenal cortex, lesions of the ovary and nonhormonal entities. The close proximity of the fetal anlagen of the gonads and adrenal cortex in the urogenital fold is often paralleled by a striking similarity in the physiologic disturbances produced by lesions of these organs. Therefore, despite the remoteness of the possibility that the pelvic mass is an incidental finding, it is important to mention both hyperplasia and tumor of the adrenal cortex, if only to dispose of them summarily. The commonest cause of the adrenogenital syndrome in a patient of this age is congenital hyperplasia of the zona reticularis. Since the hyperplasia begins in the prenatal life, the virilization has several distinctive features. The clitoris is hypertrophied at birth and a urogenital sinus is present. Stature tends to be short because the premature and excessive androgen production accelerates the rate of epiphyseal closure. Since none of these features are present in the patient, I shall exclude adrenal hyperplasia. The growth spurt beginning at the age of eleven years would be more compatible with the presence of an adrenal tumor than with hyperplasia. However, the normal 17-ketosteroid excretion constitutes strong evidence against this diagnosis. Although some adrenal tumors are accompanied by a normal 17-ketosteroid excretion, the majority are associated with one that is distinctly, and often spectacularly, elevated.

Of the many tumors and tumor-like conditions of the ovary that may be responsible for virilization, the commonest is the arrhenoblastoma. One is tempted to ascribe the patient's abnormalities to the presence of this tumor, because it could

*Assistant physician, Massachusetts General Hospital.

produce all the physical signs noted and particularly because it is sometimes associated with a normal 17-ketosteroid excretion. Regrettably, few of the patients harboring this lesion have been adequately studied from a hormonal point of view. However, a handful have shown a slightly elevated 17-ketosteroid excretion or one at the upper limits of normal, and a few have shown a level of excretion well within the limits of normal. Presumably in the latter cases there is a qualitative abnormality in the 17-ketosteroids or else the urine contains masculinizing steroids that lack the 17-carbonyl group and that therefore escape detection when assayed by chemical means. However, two points tell heavily against the diagnosis of arrhenoblastoma — the age of the patient and the elevated FSH level. This tumor is excessively rare in the pubertal age group and, more importantly, it is not associated with high levels of FSH excretion. The FSH assays that have been performed in a few cases of arrhenoblastoma have been in normal amounts or not demonstrable at all.

Another ovarian lesion to be considered is the so-called "adrenal-like" tumor of the ovary. Women harboring this tumor may be strikingly virilized. However, the virilism is not commonly of the pure type observed in this patient; there is usually, in addition, an admixture of such features of Cushing's syndrome as hypertension, osteoporosis, impaired glucose tolerance and livid striae.[1] Although a number of these features were not specifically looked for in the patient, the complete absence of any suggestion of Cushing's syndrome militates against a diagnosis of "adrenal-like tumor."

The next set of lesions of the ovary is an interesting and rather new group recently discussed by Sternberg[2] — hyperplasia and tumor of the ovarian hilus cells. Cells that are morphologically identical with the Leydig cells of the testis can be demonstrated in the hilus of the normal human ovary. These cells contain lipochrome pigment and crystalloids of Reinke and are thought to be the source of ovarian androgen. Hyperplasia and tumors of these cells have, in rare cases, been associated with virilism attended by a normal or only slightly elevated excretion of 17-ketosteroids. A hilus-cell lesion is a tempting diagnosis in this patient. However, one is deterred by the fact that in the handful of cases so far reported none of the tumors were palpable; the enlargement of the ovary was so slight that the patient was explored merely because of the virilization, and the tumor was an incidental finding. Moreover, these tumors have occurred either in women in the immediately premenopausal age group or in those well past the climacteric.

A final ovarian lesion I should like to consider is the interesting and rare condition called hyperthecosis of the ovary.[3] This lesion, characterized pathologically by overgrowth of the ovarian stroma and theca luteinization, may be associated with true virilization despite a normal level of 17-ketosteroid excretion. However, this disturbance affects both ovaries equally and would not give rise to a unilateral pelvic mass.

Inasmuch as none of the conditions so far mentioned appear to provide a satisfactory explanation for the disturbances presented by this patient, I am driven to consider a possibility that could be called remote, or perhaps even desperate. That is, that we are not dealing with an endocrine abnormality but with a problem of genetic intersexuality — that the patient was a genetically male hermaphrodite of the internal type and not a female virilized by malign androgenic influence at the time of puberty. The malformed gonads of hermaphrodites sometimes give rise to a tumor, the dysgerminoma. Could such a tumor be the mass felt in this patient's pelvis? So compatible with the case are the clinical features of this tumor that they exert a diagnostic attraction that is irresistible. The dysgerminoma is pre-eminently a tumor of early life, hence the appellation "carcinoma puellarum." The dysgerminoma has occasionally been found to be associated with an elevated level of FSH and a normal level of 17-ketosteroid excretion. Dysgerminomas have a predilection for the right ovary. In Seegar's[4] series, 48 per cent of dysgerminomas were in the right ovary, 26 per cent were bilateral and only 26 per cent were in the left ovary. Since, from comparative anatomy, it is known that in birds the right ovary always remains comparatively undifferentiated it seems permissible to infer that in a *rara avis* the right ovary is the logical progenitor of a tumor such as the dysgerminoma, which arises from undifferentiated cells.

I shall hazard the prediction that the patient was an internal hermaphrodite who harbored a dysgerminoma of the right ovary.

DR. FRANCIS INGERSOLL: Could this just be a testicle that was still in the body and that was somewhat enlarged and very easily felt?

DR. MCARTHUR: I cannot exclude that.

DR. FULLER ALBRIGHT: The positive FSH would be against it.

We saw this patient many years ago. We did not do as well as Dr. McArthur did. We got off to a bad start; she was a student nurse and came in stating that she had an arrhenoblastoma. She had a tumor of the ovary, a large clitoris and hirsutism. We easily jumped to the conclusion that she did have an arrhenoblastoma.

An arrhenoblastoma is an ovarian tumor of testicular origin. The testes, we believe, produce two hormones: one from the Leydig cells and one from the tubules. The latter inhibits production of follicle-stimulating hormone. We were surprised, therefore, to find an increased amount of FSH in the urine. This seemed to be against the diagnosis of arrhenoblastoma. The facts did not fit the theory and we concluded that the theory was wrong. Our preoperative diagnosis remained arrhenoblastoma.

CLINICAL DIAGNOSIS

Arrhenoblastoma.

DR. MCARTHUR'S DIAGNOSIS

Dysgerminoma, right ovary.

ANATOMICAL DIAGNOSIS

Dysgerminoma (seminoma) of right gonad mixed with either granulosa-theca or Sertoli-Leydig elements.

*PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This patient was operated on by Dr. Joe V. Meigs about ten years ago; he found a large right-ovarian tumor, which he removed. No gonadal tissue was identified on the left.

Dr. Scully, who is particularly interested in ovarian tumors, will discuss the pathological findings.

DR. ROBERT E. SCULLY: The tumor was a coarsely lobulated, solid, yellowish mass, the size of a tennis ball; on section it had a fish-flesh appearance. Microscopically, the tumor was composed predominantly of diffusely arranged large clear cells rich in glycogen. The stroma contained an abundance of lymphocytes as well as granulomas composed of epithelioid cells and giant cells of the Langhans type. So far, the gross and microscopical features are very characteristic of the ovarian dysgerminoma or the testicular seminoma. In certain portions of the tumor, however, the clear cells were arranged in compact cords and nests and were mixed with smaller cells, the morphology

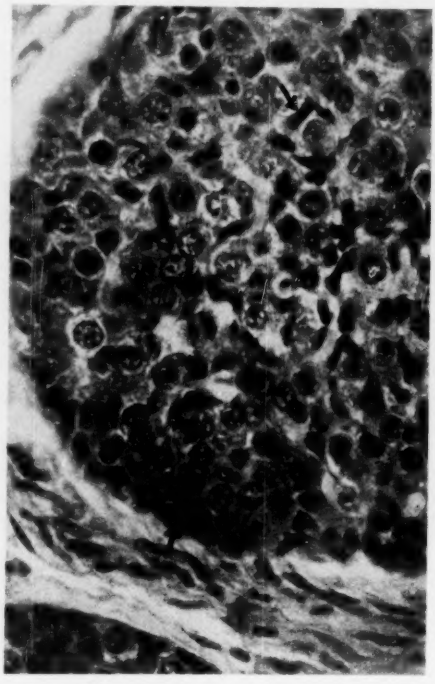


FIGURE 1. *Photomicrograph of Tumor.*
Arrows point to cells resembling granulosa cells. Large round cells are dysgerminoma cells.

of which suggested granulosa or Sertoli cells (Fig. 1). The stroma in these areas was often quite cellular and contained large polyhedral cells having the structure of steroid-hormone-producing cells of either theca or Leydig type (Fig. 2). From a morphologic viewpoint we were unable to say with certainty whether the atypical element of the tumor represents granulosa-theca neoplasia or arrhenoblastoma. As to the genetic sex of the patient, I do not think we can give a definite answer; the speci-

men we received was composed almost entirely of tumor. There were no definitive testicular or ovarian elements. The capsule contained tissue that

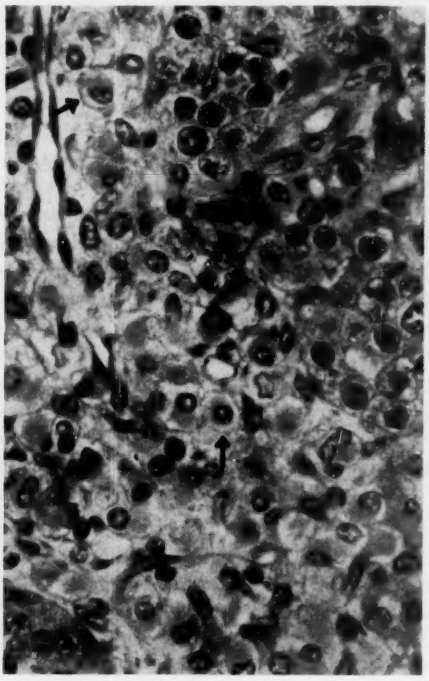


FIGURE 2. *Photomicrograph of Tumor.*
Arrows point to Leydig or theca-like cells. Large round cells in right upper field of picture are dysgerminoma cells.

resembled ovarian stroma; however, this type of tissue may be found in the testes of pseudohermaphrodites as well as in ovaries.

The postoperative follow-up on the patient has been of some value in elucidating the nature of the tumor. Although there has been no regression of the virilizing manifestations, the 17-ketosteroid-excretion level showed a decided drop, which was sustained for a longer period of time than expected for the nonspecific decrease following operative trauma.[5] The levels later rose somewhat but remained slightly lower than preoperatively. These findings suggest that the tumor was contributing to the 17-ketosteroid level, presumably by producing androgens. The FSH level remained positive postoperatively and on one occasion, when tested quantitatively, was positive for 50, 80 and 100 m.u. per 100 cc. This postoperative increment in the FSH elevation was accompanied clinically by the advent of hot flashes. Again, the FSH picture suggests that the tumor had been producing a hormone capable of inhibiting pituitary gonadotropin output to some extent.

With all the evidence in, we are concluding that the tumor was a dysgerminoma intimately mixed with an androgen-producing neoplastic element. Whether the androgen-secreting cells were theca cells or the Leydig cells of an arrhenoblastoma is impossible to say.

The patient was last seen six and a half years postoperatively; at that time she showed no evidence of recurrence of tumor.

REFERENCES

1. Kepler, E. J., Dockerty, M. B., and Priestley, J. T. Adrenal-like tumor associated with Cushing's syndrome (so-called masculinovoblastoma, luteoma, hypernephroma, adrenal cortical carcinoma of ovary). *Am. J. Obst. & Gynec.* **47**:43-62, 1944.
2. Sternberg, W. H. Morphology, androgenic function, hyperplasia and tumors of human ovarian hilus cells. *Am. J. Path.* **25**:493-521, 1949.
3. Rottino, A., and McGrath, J. F. Hyperplasia and luteinization of ovarian stroma associated with masculinization. *Am. J. Obst. & Gynec.* **45**:863-868, 1943.
4. Seegar, G. E. Ovarian dysgerminoma. *Arch. Surg.* **37**:697-725, 1938.
5. Forbes, A. Personal communication.

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COMMISSIONER OF MENTAL HEALTH

MASSACHUSETTS has had a proud record in the field of mental health and particularly in the quality of men who have worked in her state hospitals. Great was the dismay, therefore, when a little over a year ago Dr. Clifton T. Perkins resigned as commissioner of mental health to accept a similar post in Maryland. The impression was unmistakable that Massachusetts was losing its position of leadership in that field. The situation was further complicated by the fact that Dr. Perkins, with the backing of the Governor, was well launched on a five-year development program that included construction of new facilities for children and for tuberculous patients, the hiring of additional personnel, increased wages, and, perhaps of greatest importance, the inauguration of a co-ordinated program of graduate training in psychiatry under the aegis of a training faculty drawn from all three of the medical schools in the State. Dr. Perkins summarized the 1949 report of his department with the phrase "We are on our way." The magnitude of the job is indicated by the 1950 budget of $32,298,200.00 for operation and maintenance and $17,413,800.00 for new construction.

In the difficult task of picking a successor to Dr. Perkins, Governor Dever has sought the best available professional advice and has backed legislation that increases the salary of the commissioner and also makes for more effective administration of the office. The Governor is to be congratulated on his appointment of Dr. Jack R. Ewalt of Houston, Texas, as the new commissioner. Dr. Ewalt comes to this high office with a broad background of clinical administrative and teaching experience. Born in Medicine Lodge, Kansas, he graduated from the University of Colorado School of Medicine in 1933. He taught psychiatry at the University of Colorado and later at the University of Texas, where he was a full professor. From 1945 to 1950 he was also director of the Psychopathic Hospital of the University of Texas and administrator of the Medical Branch hospitals of the university. Since 1950 he has been dean of the Postgraduate School of Medicine in Houston, Texas. He has contributed extensively to the literature in his field and is co-author, with Drs. Strecker and Ebaugh, of a well known text in psychiatry.

With the helm in such capable hands, the Department of Mental Health should ride through any heavy weather that may lie ahead. To the new skipper, our salutations and best wishes.

FEAST OF REASON

THE second international assembly of medical editors, so far as the record goes, convened in Stockholm on September 21, as the final event of the fifth General Assembly of the World Medical Association. The first of these editorial convocations had taken place the year previously in New York under the same auspices, and was considered so successful as to warrant making it a regular feature of the larger annual gathering; the third meeting is planned

for a year hence as a part of the sixth World Medical Association Assembly, which is to be held in Athens.

Over eighteen journals published in more than a dozen countries were represented by their editors, three American publications being included in the list — the *Journal of the American Medical Association*, the *United States Armed Forces Medical Journal* and the *New England Journal of Medicine*. The *World Medical Association Bulletin*, though published in the United States under the able editorship of Morris Fishbein, is printed in three languages and is obviously international in scope and interest.

Many of the council members, delegates and observers of the World Medical Association were present also at the gathering of editors, making it one of the most largely attended meetings of the entire Assembly. This attendance may or may not have been stimulated by the prospect of the sumptuous Swedish luncheon, tendered by the Nepera Chemical Company of Yonkers, New York, that followed the conference.

Four papers, with their discussion, occupied the morning. Dr. Otto Leuch of Zurich, Switzerland, editor of *Bulletin Professionel des Médecins Suisses*, spoke on "Official and Scientific Medical Journalism," the "official" representing the political or "trade-union" side of journalism, with a faint implication that the two are not entirely compatible. Dr. Leuch expressed the belief that the most attentive readers of a journal's correspondence columns are the promoters of social security, in quest of ammunition.

Dr. W. R. Feasby, editor of the *Ontario Medical Review*, warned that the survival of present methods of medical journalism, — as well, indeed, as the continuance of the journals themselves, — is at stake, so sharp is the competition for the reader's time as well as for his dollars. Questionnaires in Canada have shown that reader interest favors first the editorials, then, in order, the case quizzes, the book reviews, the medical-society news and finally the advertisements and personal items.

The design of a medical journal was discussed by Dr. H. A. Shapiro, editor of the *South African Medical Journal*, in an excellent discourse, with illustrations, on the values of paper, type face and format.

Dr. Austin Smith, editor of the *Journal of the American Medical Association*, spoke on the broad subject of the "Responsibilities of Reader, Author and Publisher," expressing the belief that a journal need not be strictly scientific or entirely organizational in character but can serve both functions. This convicition is shared by the owners, the publishers and the editorial board of the *New England Journal of Medicine*.

THE OLD FARMER RETURNS

Approximately two years ago, at about the current time of year, the function of the *Old Farmer's Almanac(k)* in interpreting New England to those persons living in the more remote parts of the country that lies outside its borders was expanded on in these pages. This famous almanac(k), salty though coming from the interior and published, fittingly enough, in a place called Dublin (New Hampshire), still dispenses nearly all the information that any Yankee needs in his annual progress through the seasons.

In its hundred and sixtieth edition the weather for the coming year is predicted from day to day and from week to week and from month to month with that same astonishing accuracy that has characterized the forecasts of the Almanac(k) for a hundred and fifty-nine years. The farmer, moreover, is warned of the eclipses that may occur with startling suddenness during the year, and postal rates for all foreign countries are presented on a page not too far distant from that containing the list of state farm-extension directors.

A philosophical foreword emanating apparently from the pen of Robert B. Thomas, the original proprietor of the Almanac(k), in 1792, — for it bears his signature, — establishes a model for editorial material of this nature. In a dissertation on the diverse problems of the day and mankind's so far unsuccessful search for happiness, the following incontrovertible conclusion is contributed:

> Concurrently, in our pursuit of happiness, we are also finding that the more power and money we grant to our Federal and State and City and Town governments to carry out our wishes in these regulatory respects for the benefit of *all* of us, the nearer we approach confiscatory taxation and socialism. It could be that Education will be far more effective in bringing us to the happy existence than will the current emphasis on Regulation.

Nor is the question-and-answer department neglected, for the request of Mrs. B. D. R. of Spokane, Washington, for information about where to buy a stone-jug foot warmer to replace her electric heating pad is referred to the Society for the Return of the Double Bed.

The hats of its readers are again doffed to this perennial New England annual, as it might be dubbed in Dublin.

SELECTION OF THE FITTEST

BETWEEN now and next spring another increment of the group of physicians who will be practicing ten, twenty and thirty years from now will be selected by the admissions committees of the medical schools. They will be a small minority of the candidates who are applying. Perhaps one in four may hope to be accepted, and the opportunity to study medicine will be denied 75 per cent of all applicants.

On what basis are the arbiters of these men's destinies exercising their rather awful responsibility?

On grades? Yes, partly. On successful ratings in medical-aptitude tests? Yes, partly. On letters of recommendation from the family physician, college deans and professors and others whose opinions are presumably trustworthy? Naturally. On intellectual and moral integrity? Of course, in so far as this may be determined. On the color of their political opinions? Well, hardly, if those liberties that were guaranteed by the Constitution are still in effect.

Not so long ago the freshmen in our medical schools comprised simply those young men who for any reason whatsoever wanted to study medicine. Those who graduated were the survivors of an eliminative process that was based on accomplishment in competition with their fellows. The percentage of those who eventually succeeded in their profession did not differ greatly from what it is now, when the selection is made in advance. The difference is that almost all the selected candidates now graduate from medical school, except those who are weeded out because of physical or psychologic disability. The older system is no longer feasible, largely because the expense of training all applicants would be prohibitive, and practice could not absorb all those who graduated, despite the "doctor shortage" propaganda. It may be unfortunate, but it is no longer true that Mark Hopkins on one end of a log and a student at the other constitute a university.

But that's the way the ball bounces, as the undergraduates say. Fortunately, regardless of the manner of selection, a majority of medical graduates have carried on the practice of medicine in a generally creditable manner, and without doubt will continue to do so. So far, no one can say that cream from the separator is any better than that which rises naturally to the top.

Dr. Bradbury, of Oldtown, Me., has recently amputated the thigh at the hip joint, disarticulating the joint. This is a most perilous operation in surgery, and one that has been but a few times successfully done in this country.

Boston M. & S. J., *December 10, 1851*

OBITUARY

HENRY ASBURY CHRISTIAN

(1876–1951)

Dr. Henry Asbury Christian died suddenly at Whitefield, New Hampshire, on August 24, in his seventy-sixth year. He was born in Lynchburg, Virginia, on February 17, 1876, a descendant of Thomas Christian, who first settled in that state in 1657. After graduating from Randolph–Macon College he entered Johns Hopkins Medical School, receiving his degree in 1900. He then came to Boston, where he spent the remainder of his professional life.

Dr. Christian was one of the early group of physicians who came to Harvard from Johns Hopkins at the turn of the century and wielded such tremendous influence on the teaching of medicine at Harvard Medical School. In Boston he was first associated with the late Dr. Frank B. Mallory, at the Boston City Hospital's Department of Pathology, after which he worked with Dr.Reginald Heber Fitz at the Massachusetts General Hospital, when clinical clerkships for undergraduate students were first introduced. From 1907 to 1912 he was physician-in-chief at the Carney Hospital. Most of his professional life, however, was spent at the Peter Bent Brigham Hospital, where he became the first physician-in-chief in 1913, holding that position until his retirement in 1939. During the years 1908 to 1939 he was Hersey Professor of the Theory and Practice of Physic at Harvard Medical School.

During the first world war he was a major in the Medical Reserve Corps. Later he was active in the National Medical Research Council and for a period was in charge of the control of a severe

typhoid epidemic that was sweeping through the city of Salem, Ohio. After the beginning of World War II, when he had already retired from his official positions, he returned to duty, acting from 1942 to 1946 as clinical professor of medicine at Tufts College Medical School and visiting physician at the Beth Israel Hospital.

In addition to his other obligations, Dr. Christian was active as an author and editor. Although he maintained a major interest in diseases of the heart and kidneys, his writings and studies covered the general field of internal medicine. He published a textbook, *The Diagnosis and Treatment of Diseases of the Heart*, and edited several editions of the well known *Osler's Practice of Medicine*, as well as the *Oxford System of Medicine*.

Well merited honors came to him during his lifetime; he received the degree of Sc. D. from Jefferson Medical College and from the University of Michigan, that of LL.D. from Western Reserve University, that of D.S.M. from the American Medical Association and an honorary fellowship from the Royal College of Physicians of Canada. He was one of the founders of the American Society for Clinical Investigation, of which he was president in 1919; he was president of the Association of American Physicians in 1935 and was at one time president of the Interstate Post-Graduate Medical Association.

Throughout his life Dr. Christian, who in the hospital was affectionately called "the Professor" or, more intimately, "Uncle Henry," was interested in promising young medical men. Realizing that many capable young internists were unable to become members of the American Society for Clinical Investigation, he founded an auxiliary group, the American Federation for Clinical Research, which was nicknamed "the Young Men's Christian Association." As a physician, he was a meticulously careful observer and was quick to see clinical entities that were peculiar or discrete. Certain syndromes that bear his name, like Hand–Schüller–Christian disease, attest to his clinical acuity.

As important as Dr. Christian's clinical studies and writings were his administrative contributions. At the youthful age of thirty-two, when he became dean of Harvard Medical School, he was among the early leaders in stimulating in the faculty the spirit of medical research — not an easy task forty years ago. A greater accomplishment was the development of the medical clinic of the Peter Bent Brigham Hospital, which, as a result of his wisdom and foresight, immediately attained eminence in the medical world.

Among Dr. Christian's many useful innovations at the Brigham Hospital, one of the most pleasant and valuable was the custom of having an annual physician-in-chief *pro tempore*. He would invite an outstanding physician from this country or Europe to live at the hospital for one week and assume his duties. In this way the hospital's staff and visiting physicians were privileged to know many of the leading medical personages of the world. During that week "the Professor" would give one of his noteworthy dinners, which became celebrated in medical circles. These social occasions revealed his warmheartedness and hospitality, enabling the young interns and residents to see the sincere man beneath the official austerity.

American medicine will always be indebted to Dr. Christian for his devotion to the highest ideals of the profession and for his enduring interest in the welfare of young medical men.

S. L.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

MALLORY — Tracy B. Mallory, M.D., of Needham, died on November 11. He was in his fifty-sixth year.

Dr. Mallory, who graduated from Harvard Medical School in 1921, was chief of pathology and bacteriology at Massachusetts General Hospital and professor of pathology at Harvard Medical School. He was a former president of the New England Pathological Society and of the International Association of Medical Museums.

His widow, a son and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1951

RÉSUMÉ

DISEASE	OCTOBER 1951	OCTOBER 1950	SEVEN-YEAR MEDIAN
Chancroid	3	1	1
Chicken pox	237	399	370
Diphtheria	9	9	19
Dog bite	936	986	866
Dysentery, bacillary	13	15	15
German measles	60	105	52
Gonorrhea	207	260	334
Granuloma inguinale	0	0	0
Lymphogranuloma venereum	0	0	1
Malaria	16	1	4
Measles	403	126	274
Meningitis, meningococcal	4	6	6
Meningitis, Pfeiffer-bacillus	1	8	3
Meningitis, pneumococcal	0	1	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	5	6	4
Mumps	654	275	326
Poliomyelitis	23	123	117
Salmonellosis	20	3	10
Scarlet fever	127	151	243
Syphilis	246	111	322
Tuberculosis, pulmonary	161	148	228
Tuberculosis, other forms	10	11	16
Typhoid fever	4	1	2
Undulant fever	2	3	3
Whooping cough	267	245	314

COMMENT

The diseases notably above the seven-year median for October are malaria, measles, mumps and salmonellosis. Most of the malaria cases were reported from military hos-

pitals and represent relapses in men returning from Korea and service in other foreign countries.

Diseases below the seven-year median for the month are chicken pox, diphtheria, poliomyelitis, scarlet fever and whooping cough.

The 9 cases of diphtheria represent the third lowest figure ever reported for this month in Massachusetts.

Twenty-three cases of poliomyelitis for October, 1951, make up the lowest number of cases reported for that month in eight years. This incidence is significantly below that of September, 1951, when 68 cases were reported.

Six hundred and fifty-four cases of mumps constitute the highest number ever reported for the month of October in the state; the number of salmonellosis cases is the second highest for this month in our records.

Geographical Distribution of Certain Diseases

Anthrax was reported from: Lowell, 1.

Diphtheria was reported from: Cambridge, 1; New Bedford, 7; Wilmington, 1; total, 9.

Dysentery, bacillary, was reported from: Boston, 7; Danvers, 5; Wellesley, 1; total, 13.

Encephalitis, infectious, was reported from: Worcester, 1.

Hepatitis, infectious, was reported from: Fall River, 1; Wrentham, 2; total, 3.

Malaria was reported from: Boston, 3; Fort Devens, 10; Murphy General Hospital, 3; total, 16.

Meningitis, meningococcal, was reported from: Boston, 1; Salem, 1; Springfield, 1; Worcester, 1; total, 4.

Meningitis, Pfeiffer-bacillus, was reported from: Haverhill, 1.

Meningitis, *E. coli*, was reported from: Boxford, 1.

Meningitis, undetermined, was reported from: Brockton, 1; Cambridge, 1; Springfield, 1; Walpole, 1; Worcester, 1; total, 5.

Poliomyelitis was reported from: Arlington, 1; Barnstable, 1; Billerica, 1; Boston, 3; Cambridge, 2; Framingham, 2; Georgetown, 1; Malden, 1; Milford, 1; Newburyport, 1; Newton, 1; Northbridge, 1; Oxford, 1; Scituate, 1; South Hadley, 1; Waltham, 1; Watertown, 1; Whitman, 1; Worcester, 1; total, 23.

Salmonellosis was reported from: Boston, 1; Dartmouth, 1; Fall River, 1; Lunenburg, 1; Marblehead, 1; Needham, 1; New Bedford, 3; Peabody, 1; Revere, 1; Rockland, 1; Stockbridge, 1; Taunton, 5; Worcester, 2; total, 20.

Septic sore throat was reported from: Boston, 1; Lee, 1; Medford, 1; Worcester, 4; total, 7.

Tetanus was reported from: Wilmington, 1.

Trichinosis was reported from: Belmont, 1; Boston, 1; Fall River, 1; Norwood, 1; total, 4.

Typhoid fever was reported from: Beverly, 1; Boston, 2; Waltham, 1; total, 4.

Undulant fever was reported from: Palmer, 1; West Stockbridge, 1; total, 2.

MISCELLANY

THE RETINA FOUNDATION

The Retina Foundation, established in April, 1950, has now been organized as a new basic research unit of the Massachusetts Eye and Ear Infirmary. The Foundation, located at 30 Chambers Street, Boston, includes laboratories for biochemistry, electron microscopy, tissue culture and optics. The members of the staff are: Charles L. Schepens, M.D., director, an ophthalmologist interested in clinical work in retinal detachment; E. A. Balazs, M.D., associate director, a histochemist interested in the study of mucopolysaccharides and tissue growth; Marie A. Jakus, Ph.D., a biologist interested in the study of fine structure; and F. Wachendorf, D. Eng., a physicist specializing in optics.

The members of the Research Advisory Committee of the Foundation are: T. Gundersen, M.D., chairman; P. Boeder, Ph.D.; P. A. Chandler, M.D.; W. J. Crozier, Ph.D.; P. Heath, M.D.; and B. Sachs, M.D.

The work of the Retina Foundation was supported in its initial stages by the Veterans Administration. It has since received grants from the United States Public Health Service, the American Optical Company, the Kresge Foundation, the G. M. Hyams Fund, Incorporated, the Vivian B. Allen Foundation, the National Council to Combat Blindness, Incorporated, the Office of Naval Research and the Committee of the Permanent Charity Fund, Incorporated. It is also supported by private donations.

CHANGE IN FORMS BY VETERANS ADMINISTRATION

Physicians who treat Veterans Administration beneficiaries will find January authorizations on a new form that has been adopted for nationwide use. Different forms have been tried on a test basis, and the one selected has been successfully used in a midwestern state for some time. The new forms should not prove to be confusing, and they will be of aid in simplifying governmental audit procedures.

For each authorized patient 3 copies of VA Form 10-2568a ("*Authorization and Invoice*") will be sent to the physician. One copy will be stamped "This copy for your files." On the right-hand side the date of treatment, the type of visit (office, home or hospital) and the fee should be indicated, with the total cost in the grand-total block. Two copies will be returned to the Veterans Administration; the physician will sign only one, which constitutes his bill for services rendered.

The physician will also receive one copy of VA Form 2690b ("*Report of Medical Treatment Rendered and Request for Continue Treatment.*") This form has a detachable section on which to request further treatment. The upper part of the form is to be completed, listing in detail treatment and the medication prescribed. This should be returned to the Veterans Administration promptly after administration of the last treatment that is covered by the authorization.

No form will be provided for prescriptions. The Veterans Administration requests these in duplicate on the physician's blank. The following certificate must be written and signed by the physician: "I am authorized to treat and prescribe for the above-named Veterans Administration patient." Prescriptions, may, as previously, be filled in the Veterans Administration pharmacy when inconvenience or suffering on the part of the veteran is not involved.

If the veteran is entitled to travel allowance he will present a copy of Veterans Administration Form 3-3542a. The physician should complete Certificate 1, indicating the dates on which the veteran reported, sign it and have it returned to the Veterans Administration. The beneficiary cannot collect travel expenses unless this form is returned completed by the physician.

On December 1 the Veterans Administration will mail instructions and sample copies of these forms to all fee-basis physicians.

BOOK REVIEWS

The Life and Times of Gaspare Tagliacozzi, Surgeon of Bologna, 1545-1599, with a documented study of the scientific and cultural life of Bologna in the sixteenth century. By Martha T. Gnudi and Jerome P. Webster. With a preface by Arturo Castiglioni. 4°, cloth, 538 pp., with 76 plates. New York: Herbert Reichner, 1951. $15.00.

This biography of the father of plastic surgery contains also a short history of the subject from the times of Susruta, Celsus and Galen, beginning about the sixth century B.C., to the work of Tagliacozzi, 1586–1597. Pertinent excerpts from the books of these famous physicians have been translated into English and interspersed throughout the chapter.

The *De curtorum chirurgia per insitionem* was published in Venice by Bindoni in 1597. The author had been at work on his manuscript since 1586 and it was finally given to the press two years before his death. A pirated edition was printed by Meietti in the same year, and later editions were issued at Frankfurt in 1598 and Berlin in 1831.

Succinct abstracts in English of Books 1 and 2 on the theory and practice of plastic surgery are provided in the chapter on the book, as well as the complete translation of Book 2 by Alexander Read, reprinted from his *Chirurgorum*

comes. . ., London, 1687. The original plates, 22 in all, have been reproduced from the first edition.

The original editions are very scarce, and this excellent book serves as a worthy substitute for interested persons.

The biographical material is detailed, covering the period from the birth to the death of Tagliacozzi. The publishing is excellent in every way. The paper is soft, with a non-glare finish, the type is large and easily readable, the margins are large and the plates are fine. There is a bibliography of 359 titles and an index of 22 pages. The price is modest for such a de luxe volume.

JAMES F. BALLARD

A Bibliography of Infantile Paralysis, 1789–1949: with selected abstracts and annotations. Prepared under the direction of The National Foundation for Infantile Paralysis, Inc. Edited by Morris Fishbein, M.D., editor, Excerpta Medica, and Ella M. Salmonsen, chief, Medical Department, John Crerar Library, Chicago. With Ludvig Hektoen, M.D. Second edition. 4°, cloth, 899 pp. Philadelphia: J. B. Lippincott Company, 1951. $16.00.

When the first edition of *A Bibliography of Infantile Paralysis*, covering the years from 1789 to 1944, was published in 1946, plans were already made to keep this compilation up to date. The book has now been extended through the year 1949, and opportunity has been taken to make additions to the contributions made in previous years, along with some corrections. The work has now extended to nearly 900 pages. A complete index, by both author and subject, is included, adding greatly to the value of the bibliography. A large percentage of the references are given in abstract, with annotations. The book is an excellent example of co-operative research by the chief editor, a qualified medical-reference librarian, and a distinguished scientist. The editors, the publisher and particularly the National Foundation for Infantile Paralysis should be congratulated on the new edition of this indispensable book so widely used by the medical profession, librarians, public-health officials and others. Nothing of its kind existed, in such comprehensive form, before the first edition was published in 1946. The reputation for accurate abstracting already established has been upheld in the new edition.

The years 1945–1949 have been a productive period in the investigation of poliomyelitis. Seventeen hundred and fifty reports are listed as having been written during these five years. Many deal with the problem of poliomyelitis viruses and their differentiation into immunologic types. As one reads through the list of contributions since 1944, an impression is gained of the value of the National Foundation for Infantile Paralysis in the advancement of our knowledge of this disease. A considerable percentage of the authors conducted their research under the sponsorship of the foundation. Much of the clinical work, too, was guided by foundation direction; and the International Congresses, the second of which was held in Copenhagen in 1951, indicate the wide interest shown by the Foundation in the stimulation of poliomyelitis investigation. This book, therefore, not only is a tribute to the foundation as one of its finest publications but also indicates something of the scope of the activities of this organization devoted to overcoming one of the most tragic of diseases and one that has become increasingly widespread in the last few years.

HENRY R. VIETS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Handbook of Medical Management. By Milton Chatton, M.D., instructor in medicine, University of California Medical School, Sheldon Margen, M.D., clinical instructor in medicine, University of California Medical School, and Henry D. Brainerd, M.D., assistant clinical professor of medicine and pediatrics, University of California Medical School, assistant clinical professor of pediatrics, Stanford University School of Medicine, and physician in charge, Isolation Division, San Francisco Hospital. Second edition. 12°, cloth, 507 pp., with tables. Palo Alto, California: University Medical Publishers, 1951. $3.00.

This second edition of a handbook first published in 1949 has been brought up to date by incorporating new material of 1950. Most of the chapters have been revised and the volume has been increased in size. It includes new material on ACTH, cortisone therapy, endocrine disorders, the newer antibiotic drugs, vitamin B_{12} and other subjects. The drugs mentioned in the text have been brought to conformity with the 1950 *United States Pharmacopoeia* and *New and Nonofficial Remedies 1950*. There has been a careful deletion of nonessential and outmoded data. The practice of printing important material inside the front and back covers should be discouraged, especially as the volume will have considerable use. There is a good index, and the publishing is excellent.

Cybernetics: Circular, causal and feedback mechanisms in biologic and social systems. Transactions of the Seventh Conference, March 23–24, 1950, New York. Edited by Heinz von Foerster, Department of Electrical Engineering, University of Illinois. Assistant editors: Margaret Mead, American Museum of Natural History, New York, and Hans L. Tueber, Department of Neurology, New York University College of Medicine. 8°, cloth, 249 pp., with 28 illustrations. New York: Josiah Macy, Jr., Foundation, 1951. $3.50.

This new volume of a standard series contains eight papers on varying subjects. Two papers may be especially noted: one on digital motions in the central nervous system and one on the relation of symbolic function in language formation and in neurosis.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Bard Professor of Medicine, Columbia University College of Physicians and Surgeons. Eighth edition. 4°, cloth, 1627 pp., with 204 illustrations and 40 tables. Philadelphia: W. B. Saunders Company, 1951. $12.00.

This new edition of a standard textbook on internal medicine has been thoroughly revised to bring it up to date. Twenty new subjects have been included and discussions of 82 subjects have been rewritten. The authors have succeeded in reducing the size of the book by 136 pages without sacrificing any important material. There is a comprehensive index and the book is well published. It should be in all medical libraries and should prove valuable to all practicing physicians.

Connective Tissues: Transactions of the First Conference, April 24–25, 1950, New York. Edited by Charles Ragan, Department of Medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 164 pp., with 35 illustrations and 3 tables. New York: Josiah Macy, Jr., Foundation, 1951. $3.25.

This volume contains the papers, with discussion, read at a new conference sponsored by the Josiah Macy, Jr., Foundation. The papers concern structure and function of normal connective tissue, pathology of connective tissue, fibrinoid degeneration, chemistry of connective tissue, polysaccharides, enzymatically modified ovalbumins and the effect of ACTH and cortisone on connective tissues. This new series should be in all medical libraries.

Die Moderne psychiatrische Schockbehandlung. By Prof. Dr. Med. Walter R. von Baeyer, Stadtobermedizinalrat, Vorstand der Psychiatrischen und Nervenklinik der Allgemeinen Stadtischen Krankenhauses Nürnberg. 8°, paper, 160 pp., with 3 illustrations and 3 tables. Stuttgart: Georg Thieme, 1951. DM 14.40.

This monograph on shock treatment in psychiatric disorders covers the subject, from a description of methods, including insulin, electroshock and other procedures, to a discussion of the clinical effects of treatment, including cyclic disorders and schizophrenia. An evaluation of the modern literature is correlated throughout the text, and there are a number of illustrative case histories. The text is concluded with a 5-page bibliography, and there are author and subject indexes. The monograph should be in all collections on the subject.

Spezielle Pathologie der Krankheiten des zentralen und peripheren Nervensystems. By Gerd Peters, Professor der Neurologie und Psychiatrie an der Universität Bonn. 12°, cloth, 437 pp., with 214 illustrations. Stuttgart: Georg Thieme, 1951. DM 56.

This new book on the special pathology of diseases of the central and peripheral nervous system is a thorough study of the subject. The whole field is well covered, and the pertinent literature is evaluated. There are indexes of authors and subjects. The publishing is excellent. The book should be in all collections on the subject.

The Bender-Gestalt Test: Quantification and validity for adults. By Gerald R. Pascal, Ph.D., research psychologist, Western Psychiatric Institute and Clinic, and associate professor of psychology, University of Pittsburgh, and Barbara J. Suttell, M.S., associate research psychologist, Western Psychiatric Institute and Clinic. With a foreword by David G. Wright, M.D. 8°, cloth, 274 pp., with illustrations. New York: Grune and Stratton, 1951. $6.50.

This monograph on a test devised for the determination of the present and immediate severity of psychiatric disorder is divided into three parts: quantification; clinical use of the Bender-Gestalt test; and a scoring manual. This book should be in all collections on applied psychology and psychiatry.

Syllabus of Human Neoplasms. By R. M. Mulligan, M.D., professor of pathology, University of Colorado School of Medicine. 8°, cloth, 317 pp., with 230 illustrations. Philadelphia: Lea and Febiger, 1951. $7.50.

This syllabus describes the more common human neoplasms, with a correlation of their salient clinical features. The material is arranged according to the systems of the body. Lists of references are appended to the various chapters and there is a comprehensive index.

Maternal Care and Mental Health: A report prepared on behalf of the World Health Organization as a contribution to the United Nations program for welfare of homeless children. By John Bowlby, M.A., M.D., consultant in mental health, World Health Organization, and director, Child Guidance Department, Tavistock Clinic, London. 8°, paper, 177 pp., with tables. Geneva: World Health Organization, Palais des Nations, 1951. $2.00.

This special monograph, presenting a study of maternal deprivation, discusses the subject in two parts: adverse effects and prevention. There is a bibliography of 159 titles. The lack of an index detracts from the reference value of the book.

NOTICES

ANNOUNCEMENT

Dr. John A. McGowan, Jr., announces the opening of his office for the practice of internal medicine at 1101 Beacon Street, Brookline.

HARVARD MEDICAL SOCIETY

The Harvard Medical Society will present a program on pulmonary function on Tuesday, December 11, in Amphitheatre D, Harvard Medical School, at 8:00 p.m. Dr. James L. Whittenberger will preside.

PROGRAM

Observations on Pulmonary Hemodynamics During Anoxia — Drs. Benjamin M. Lewis, Florence W. Haynes, Richard Gorlin and Lewis Dexter (Department of Medicine, Peter Bent Brigham Hospital).

Viscoelastic Properties of the Lungs During Spontaneous Breathing — Dr. Jeremiah Mead (Department of Physiology, Harvard School of Public Health).

The Mechanics of Breathing in Artificial Respiration — Dr. James L. Whittenberger (Department of Physiology, Harvard School of Public Health).

New Methods for Determining Respiratory Dead Space and Effective Alveolar Gas Composition in the Anesthetized Dog and in Man — Drs. John R. Pappenheimer, Alfred P. Fishman, and Luis Borrero (Department of Physiology, Harvard Medical School).

SYMPOSIUM ON PREMEDICAL EDUCATION

Alpha Epsilon Delta, the national premedical honor society, — in co-operation with the American Association for the Advancement of Science, Section K — Social and Economic Sciences, Subsection Nm–Medicine; the American Society of Zoologists; and Beta Beta Beta Biological Fraternity, — will hold a luncheon and symposium at the meeting of the American Association for the Advancement of Science at the Benjamin Franklin Hotel, Philadelphia, Pennsylvania on December 28. The subject of the program will be "Premedical Education and Social Health."

BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

The thirteenth British Congress of Obstetrics and Gynaecology will be held in the Riley Smith Hall of the University of Leeds July 8–11, 1952.

All who are interested in attending this congress should apply as soon as possible to Brian Jeaffreson, F.R.C.O.G., Hon. Secretary, the Hospital for Women, Country Place, Leeds, England.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 7, 14, 21 AND 28 AND JANUARY 4. New England Deaconess Hospital Clinic. Page 548, issue of October 4.

DECEMBER 8–13. American Academy of Dermatology and Syphilology. Page 752 , issue of November 8.

DECEMBER 8–22. The Springfield Hospital. Page 832, issue of November 22.

DECEMBER 10 AND 13. Lowell Institute Lectures. Page 752, issue of November 8.

DECEMBER 11. Boston City Hospital House Officers' Association. Page 832, issue of November 22.

DECEMBER 11. Harvard Medical Society. Notice above.

DECEMBER 11. Springfield Academy of Medicine. Page 874, issue of November 29.

DECEMBER 11–19. International Congress on Mental Health. Page xiii, issue of July 26.

DECEMBER 12. New England Pediatric Society. Page 832, issue of November 22.

DECEMBER 13. Pediatric Problems of the General Practitioner. Dr. James Marvin Baty. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

DECEMBER 14 AND 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

DECEMBER 28. Symposium on Premedical Education. Notice above.

JANUARY 7, FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

JANUARY 9. Essex North District Medical Society. Page 832, issue of November 22.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Notice above.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 9. Pentucket Club, 111 Main Street, Haverhill.

HAMPSHIRE

JANUARY 2. Veterans Hospital, Northampton.

MARCH 5. Cooley-Dickinson Hospital, Northampton.

MAY 7. Annual Meeting. Jones Library, Amherst.

(*Notices concluded on page xvii*)

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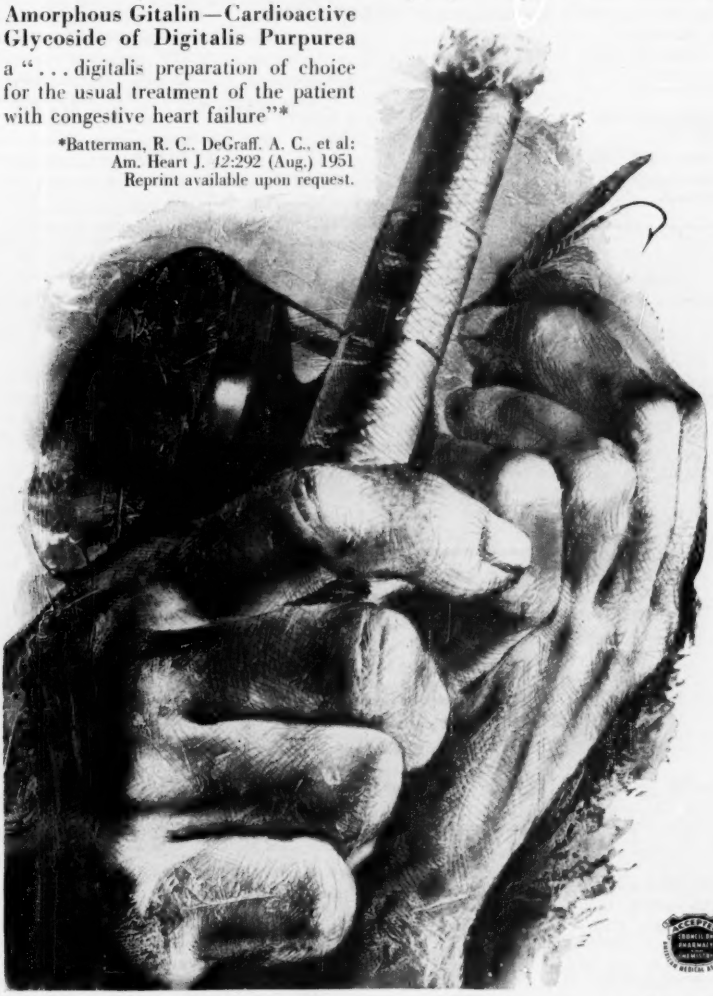
*Batterman, R. C., DeGraff, A. C., et al: Am. Heart J. 42:292 (Aug.) 1951
Reprint available upon request.



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(*Additional advertisements on page xvi*)

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	Physiologic Effects of Autonomic Discharge	
	Sympathetic	Parasympathetic
Gastro-intestinal System	Hypomotility Intestinal Atony Hyposecretion Reduced salivation	Hypermotility Gastrointestinal spasm Hypersecretion
Cardio-vascular System	Rapid heart rate Peripheral vaso-constriction	Slow heart rate Vasodilatation
Functional Manifesta-tions	Palpitation Tachycardia Elevated blood pressure Dry mouth and throat	Heartburn Nausea-vomiting Low blood pressure Colonic spasm

The data here tabulated is from references 3,4,5,6,7, given below.

When the clinical picture is suggestive of functional disorder, the diagnosis is supported by the presence of the following indications of autonomic lability:

Variable Blood Pressure
Body Temperature Variations
Changing pulse rate
Deviations in B. M. R.
Exaggerated Cold Pressure Reflex
Oculo-Cardiac Reflex Abnormalities
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Therapy in these cases is directed toward: 1) relieving the somatic disturbance to prepare the patient for psychotherapy*; 2) guidance in making adjustment to stressful situations and correction of unhealthy attitudes.

*Drug treatment using adrenergic and cholinergic blocking agents in conjunction with sedatives. [8,9,10]

1. Ebaugh, F.: Postgrad. Med. *4:* 208, 1948. 2. Wilbur, D.: J.A.M.A. *141:* 1199, 1949. 3. Williams, E. and Carmichael, C.: J. Nat'l. Med. Assoc. *42:* 32, 1950. 4. Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics, The Macmillan Co., 1941. 5. Katz, L. et al: Ann. Int. Med. *27:* 261, 1947. 6. Weiss, E. et al: Am. J. Psychiat. *107:* 264, 1950. 7. Alvarez, W.: Chicago Med. Soc. Bulletin, 581, 1950. 8. Rakoff, A.: A Course in Practical Therapeutics, Williams and Wilkins, 1948. 9. Karnosh, L. and Zucker, E.: A Handbook of Psychiatry. C. V. Mosby Co., 1945. 10. Harris, L.: Canad. M.A.J. *58:* 251, 1948.

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NOTICES (*Concluded from page 916*)

NORFOLK

JANUARY 22. Veterans Administration Hospital, West Roxbury.
FEBRUARY 26. Boston Medical Library.
MARCH 25. Boston Medical Library.
APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 13

THURSDAY, DECEMBER 13

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*12:00 m.–1:00 p.m. Guest speaker. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Medical Division Lectures. Mount Auburn Hospital, Cambridge.
5:00 p.m. Medical Education — A Concern of the People. Dr. James Howard Means. Boston Public Library.

FRIDAY, DECEMBER 14

*8:15 a.m. Renal Glycosuria. Drs. Stanton and Marble. Baker Clinic, New England Deaconess Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds, Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.
*11:00 a.m.–12:00 m. Pediatrics. Woolson II. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. New England Center Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:30 p.m. Surgicopathological Conference. Pratt Lecture Hall. New England Center Hospital.
*1:00–2:00 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–4:00 p.m. Arthritis Conference. Stearns Auditorium. New England Center Hospital.
*4:00–6:00 p.m. X-Ray Seminar. Pratt Lecture Hall. New England Center Hospital.

MONDAY, DECEMBER 17

*11:00 a.m. Obstetrical Meeting. Mount Auburn Hospital, Cambridge.
*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.
*12:00 m.–1:00 p.m. Endocrinology Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.
3:00 p.m. Gynecology Rounds. Mount Auburn Hospital, Cambridge.
*7:00–9:00 p.m. Combined Anesthesia Teaching Program of Boston. Stearns Auditorium, New England Center Hospital.

TUESDAY, DECEMBER 18

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:00 m.–1:30 p.m. Surgical Grand Rounds. New England Center Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pathological Conference. Mount Auburn Hospital, Cambridge.
4:30 p.m. House Staff — Intern–Resident Committee. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Surgical Lectures. Mount Auburn Hospital, Cambridge.
*8:15 p.m. Medical Division Meeting. Mount Auburn Hospital, Cambridge.

WEDNESDAY, DECEMBER 19

*11:00 a.m.–12:00 m. Medical Clinic (Children's Medical Center). Amphitheatre, Children's Hospital.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheatre, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Meeting. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Combined Clinic of All Services (Children's Medical Center). Amphitheatre, Children's Hospital.
*4:00 p.m. New England States Chapter of the American College of Chest Physicians and The Overholt Clinic. New England Deaconess Hospital.

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